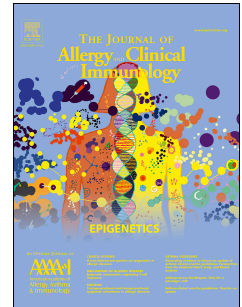


# Accepted Manuscript

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# Treatment of urticarial vasculitis: A systematic review

ACCEPTED MANUSCRIPT

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*Keywords:* urticarial vasculitis, review, treatment

*Abbreviations:*

AHs: antihistamines

AZA: azathioprine

CP: cyclophosphamide

CS: corticosteroids

CYC: cyclosporine A

IVIG: intravenous immunoglobulins

HCQ: hydroxychloroquine

HUV: hypocomplementemic urticarial vasculitis

HUVS: hypocomplementemic urticarial vasculitis syndrome

MTX: methotrexate

NSAIDs: nonsteroidal anti-inflammatory drugs

NUV: normocomplementemic urticarial vasculitis

RTX: rituximab

UV: urticarial vasculitis

Urticarial vasculitis (UV) is a difficult-to-treat condition characterized by long-lasting urticarial rashes and histopathologic findings of leukocytoclastic vasculitis. Treatment is dictated by severity of skin and systemic involvement and the underlying systemic disease. This is a comprehensive systematic review of the efficacy of current UV treatment options. We searched for relevant studies in seven databases including MEDLINE, Scopus, and Web of Science. In total, 261 eligible studies and 789 unique UV patients were included in the systematic review. Most UV patients are adult females with chronic ( $\geq 6$  weeks) and systemic disease. UV is mostly idiopathic, but can be associated with drugs, malignancy, autoimmunity and infections. It usually resolves with their withdrawal or cure. Corticosteroids are effective for the treatment of skin symptoms in  $>80\%$  of UV patients. However, their long-term administration can lead to potentially serious adverse effects. The addition of immunomodulatory or immunosuppressive agents often allows corticosteroids tapering and improves the efficacy of therapy. Biologicals, including omalizumab, as well as corticosteroids, cyclophosphamide, dapsone, mycophenolate mofetil, plasmapheresis, colchicine, hydroxychloroquine, intravenous immunoglobulins, NSAIDs, and cyclosporine can be effective for skin as well as systemic symptoms in UV patients.  $H_1$ -antihistamines, montelukast, danazol,  $H_2$ -antihistamines, pentoxifylline, doxepin and tranexamic acid are not effective in most UV patients. As of yet, no drugs have been approved for UV, and management recommendations are based mostly on case reports and retrospective studies. Prospective studies investigating the effects of treatment on the signs and symptoms of UV are needed.

## Introduction

Urticarial vasculitis (UV) is characterized by long-lasting urticarial rashes and histopathologic findings of leukocytoclastic vasculitis. It is now more than 100 years since Wills and Lond first described two young men with UV (fever, arthritis, purpura, angioedema and wheals).<sup>1</sup> In 1956, McCombs and coworkers reported two UV patients who had wheals and histological signs of vasculitis.<sup>2</sup> Since then, UV has been diagnosed in 9-21% of patients with leukocytoclastic vasculitis.<sup>3-6</sup> Also, it was reported in 2-27%<sup>7-10</sup> of patients initially presenting with urticaria.

The worldwide prevalence of UV is unknown. In the US population, the incidence of UV was found to be 0.5 per 100 000 person-years.<sup>3</sup> Median age at onset was 45 years and 70-74% of patients were female.<sup>11-14</sup> Pediatric cases are rare.<sup>6, 15, 16</sup> Only 1% of children with any type of vasculitis have UV.<sup>17</sup>

Most UV cases are idiopathic. In some patients, UV can be associated with external factors (e.g. drugs) or underlying diseases including infections, malignancy, and autoimmune or autoinflammatory disease.<sup>7, 12</sup> For example, up to 20% of patients with systemic lupus erythematosus (SLE) reportedly have UV.<sup>18</sup> The median duration was reported to be 1.5-4 years<sup>14, 19-21</sup> with estimated overall survival rates of 80% at 5 years after diagnosis.<sup>3</sup> Few fatal cases were described in underlying diseases such as malignancy.<sup>13</sup>

In addition to recurrent whealing, 9-56% UV patients can present with angioedema, purpura, pain and/or tenderness, fever, asthenia, arthralgia, lymph node enlargement, abdominal pain, ocular manifestations, dyspnea, cough and/or renal problems.<sup>13, 14, 22, 23</sup> Ear and nose involvement, pericarditis and neurologic symptoms are rare and appear in 7% patients.<sup>13</sup> Unlike chronic urticaria, in which the wheals last for several hours, urticarial lesions in UV usually persist for more than 24 h and can last for several days.

Pathophysiologically, UV is a type III hypersensitivity reaction, which results in the deposition of antigen-antibody complexes in the vascular lumina with subsequent complement activation. Based on complement consumption, UV can be divided into normocomplementemic UV (NUV), hypocomplementemic UV (HUV) and a rare hypocomplementemic urticarial vasculitis syndrome (HUVS, also known as McDuffie syndrome first described in 1973<sup>24</sup>). About 80% of all UV patients have NUV, and 9-21% patients suffer from HUV/HUVS.<sup>7, 11, 12</sup> HUV and HUVS are considered to be the most severe forms of UV. Both are often associated with a diffuse neutrophilic infiltration of lesional skin,<sup>11, 25</sup> systemic symptoms, long duration,<sup>12</sup> and underlying disorders.<sup>7, 12, 26</sup> The diagnosis of HUVS is based on urticarial lesions of >6 months duration, hypocomplementemia with low C1q, C3, C4 (major criteria) and the presence of anti-C1q, dermal vasculitis by biopsy,

Biopsy findings of skin lesions from patients with UV include erythrocyte extravasation, vascular and perivascular infiltration of polymorphonuclear leukocytes with formation of nuclear dust (leukocytoclasia), and fibrinoid necrosis of the vessel walls.<sup>3, 22, 28, 29</sup> Direct immunofluorescence can show deposition of complement components and immunoglobulins in vessel walls.<sup>5</sup>

Many different treatment strategies have been tried in UV patients, from antihistamines, corticosteroids and immunosuppressive drugs to novel biological therapies.<sup>13, 30, 31</sup> UV is notoriously hard to treat. Many drugs show limited efficacy and/or have potentially serious adverse effects. Moreover, no clinical guidelines or treatment algorithms have been published so far. Randomized clinical trials as well as approved therapies are lacking in UV. Here, we performed, for the first time, a comprehensive systematic review of the efficacy of UV treatment options.

## Search strategy

The systematic literature review was performed according to PRISMA guidelines.<sup>32</sup> The literature search of MEDLINE, Scopus, Web of Science, Biosis Citation Index, KCI Korean Journal Database, Russian Science Citation Index and SciELO Citation Index databases (from January 1940 to December 2017) was conducted using the following terms: “urticarial vasculitis” OR “hypocomplementemic vasculitis” OR “normocomplementemic vasculitis” OR “hypocomplementemic vasculitis syndrome” OR “anti-C1q vasculitis” OR “McDuffie syndrome” AND “treatment” OR “immunosuppressive drugs” OR “immunosuppressant” OR “NSAID” OR “antihistamines” OR “immunoglobulin” OR “immune globulin” OR “intravenous immunoglobulin” OR “corticosteroids” OR “corticoid” OR “glucocorticoid” OR “steroid hormone” OR “steroids” OR “prednisolone” OR “prednisone” OR “methylprednisolone” OR “azathioprine” OR “mycophenolate mofetil” OR “methotrexate” OR “cyclophosphamide” OR “dapsone” OR “colchicine” OR “hydroxychloroquine” OR “cyclosporine” OR “ciclosporin” OR “omalizumab” OR “rituximab” OR “anakinra” OR “canakinumab” OR “plasmapheresis” OR “tocilizumab”. No language filter was applied.

The aim of the review was to find all studies that address any or all of the following questions: 1) Does the treatment of underlying disease lead to UV remission? 2) What drugs are used for the treatment of UV patients? 3) How effective are the drugs used for the treatment of UV? 4) What are the drug doses and treatment duration reported in successfully treated cases?

## Study selection criteria

Studies were included in the systematic review based on the PICOS selection criteria (Suppl. Table 1). A study was considered eligible for the systematic review, if the diagnosis of UV was confirmed by skin biopsy and the efficacy of the drugs regarding skin symptoms was clearly described. In some studies, the results of skin biopsy assessment were not reported in the article, but the clinical symptoms and/or laboratory findings were strongly suggestive of UV and the authors of these studies classified the disease as UV. UV was considered acute, if the duration of the disease was <6 weeks and chronic, if the duration was ≥ 6 weeks.

## Data extraction

Three investigators (PK, MG and HB) independently searched and reviewed the titles and abstracts of all publications retrieved by the literature search (Suppl. Figure 1). Full texts of relevant studies were obtained, when available, for further assessment and were reviewed

independently by two authors (PK and MG). Disagreement in data extraction was resolved by discussion between the two authors (PK and MG) and the third author (HB) when necessary. Additional articles were found by searching lists of references from previously identified publications.

The following data were extracted, when available: author; year; country; age of patients; type of UV; presence of extracutaneous symptoms; duration of UV (less or more than 6 weeks); presence of underlying systemic disease; biopsy data; efficacy of antihistamines, corticosteroids, immunomodulatory or immunosuppressive therapy, biologicals and other drugs for the treatment of UV skin and systemic symptoms; initial dose of drug; duration of treatment; time and duration of improvement of urticarial rash; relapse of urticarial rash.

We also included data from the reports where avoidance of external factors (e.g. drugs) or treatment of underlying diseases led to the remission or improvement of UV (Suppl. Table 2).

The characteristics of the drugs successfully used are listed in the Suppl. Tables 3 and 4.

#### *Grading the response to treatment*

The term “complete cutaneous remission” was used when the cutaneous symptoms of UV, primarily lesions, disappeared completely during  $\leq 3$  months after the initiation of treatment. The term “partial cutaneous improvement” was used when cutaneous lesions did not resolve completely in response to the therapy and additional treatment was required to control the disease. UV patients were regarded as non-responders, if no improvement in skin symptoms of UV was seen during or after the treatment. Some studies included in the Suppl. Table 4 also reported the efficacy of drugs regarding systemic symptoms and laboratory parameters.

*Most UV patients are adult females with chronic and systemic disease*

In total, 261 eligible studies and 789 UV patients were included in the systematic review (Suppl. Tables 3 and 5, Figure 1). Most studies came from the USA (n=81), the UK (n=32), France (n=20), Japan (n=19), Italy (n=16) and Germany (n=15). 41 studies reported UV in more than one patient (seven prospective studies<sup>33-39</sup> and 34 retrospective studies). Most patients were adult females with chronic UV and systemic symptoms (Table 1). Underlying systemic diseases were described in 174 UV patients, mostly SLE and other autoimmune diseases, malignancy and chronic hepatitis C (Table 2). Of 99 patients with underlying diseases and known complement levels, 73% had HUV/HUVS (n=73) and 27% had NUV (n=26). At least 37 SLE patients had HUV/HUVS and at least nine patients had NUV.

*Urticarial vasculitis can be caused by drugs, malignancy and infections and can resolve with their withdrawal or cure*

The cause of UV was reportedly established in 53 patients from 50 different studies (Suppl. Table 2). 94% (46/49) patients were adults. Withdrawal of relevant drugs or occupational agents caused remission or improvement of UV in 19 patients. In seven patients, the antiviral treatment of chronic hepatitis C likely improved UV or initiated vasculitis remission associated with a cure or improvement of hepatitis. In four patients, remission of UV was seen after acute hepatitis A or B was resolved. Eleven patients with UV benefited after surgical therapy, chemotherapy and/or radiation therapy of malignant neoplasms. In two studies, antiparasitic treatment led to improvement of both internal parasitic infection and UV. Four studies reported efficacy of antimicrobial agents for treatment of UV in patients with *Mycoplasma pneumoniae*, *Mycobacteria tuberculosis* or *Trichomonas vaginalis* infection. Two UV patients benefited from levothyroxine administration due to autoimmune thyroiditis.

Acute UV was more frequently associated with drug reactions (17 of 19 patients) and acute hepatitis B (3 of 3 patients) than chronic UV, whereas chronic UV was observed in all reported patients with chronic hepatitis C and in all but one patient with malignancy and infections. Eight out of 10 patients with drug reactions had NUV.

*Corticosteroids are effective for the treatment of skin symptoms in more than 80% of UV patients*

The efficacy of corticosteroid (CS) monotherapy was evaluated in 144 studies including 295 UV patients. CS were the most effective drugs with >80% of UV patients observed improvement or

remission of skin symptoms of their UV (Figure 1). CS (monotherapy or combination with antihistamines) were ineffective in 19% (63/335) of patients with chronic UV and in 5% (1/19) of patients with acute UV.

*Biologicals, including omalizumab, can be effective for the treatment of skin symptoms of UV*

Anti-TNF (etanercept or infliximab, 5 patients in 5 studies), anti-IL1 $\beta$ /IL-1R (anakinra or canakinumab, 14 patients in 5 studies), rituximab (9 patients in 9 studies), tocilizumab (2 patients in 2 studies) and omalizumab (16 patients in 13 studies) were effective in 60-100% of UV patients treated (Suppl. Table 3). Complete remission of skin symptoms was most frequently seen in patients treated with omalizumab, tocilizumab and rituximab ( $\geq 75\%$ ).

*Addition of immunomodulatory or immunosuppressive agents allows corticosteroids tapering and improves the efficacy of therapy*

In 23 studies (25 patients), where corticosteroids were ineffective in monotherapy, addition of one or more immunomodulatory or immunosuppressive agents, namely colchicine (CLH, n=6), cyclophosphamide (CP, n=3), mycophenolate mofetil (MMF, n=3), azathioprine (AZA, n=3), methotrexate (MTX, n=2), intravenous immunoglobulins (IVIG, n=2), hydroxychloroquine (HCQ, n=2), omalizumab (n=2), rituximab (n=2), dapsone (DP, n=1), AZA and DP (n=1), plasmapheresis (n=1), anakinra (n=1) or cyclosporine (CYC, n=1) led to remission of UV or its improvement. Steroid-sparing effects were shown for HCQ, CLH, DP, MMF, CYC, AZA, omalizumab, rituximab, anakinra, tocilizumab and infliximab (Suppl. Table 3, 5 and 6).

Combinations of more than two immunomodulatory or immunosuppressive agents were used in 12 patients. They were effective in 10 patients and ineffective in 2 patients.

*Corticosteroids, CP, DP, MMF, plasmapheresis, biologicals, NSAIDs, CLH, HCQ, CYC, IVIG can be effective for skin as well as extracutaneous symptoms in UV patients*

CS, DP, MMF, plasmapheresis, CLH, HCQ, IVIG, biologicals, NSAIDs and CYC were effective for skin as well as extracutaneous symptoms such as joint, ocular, pulmonary and gastrointestinal manifestations and/or fever (Suppl. Tables 3-6). Increase in levels of complement components was seen during or after treatment with CS, HCQ, CP, DP, MMF, plasmapheresis, omalizumab and infliximab in HUV/HUVS patients. Decrease in C-reactive protein and/or ESR levels was seen during or after treatment with CS, CP, DP, canakinumab, anakinra and infliximab.

H<sub>1</sub>-antihistamines (H<sub>1</sub>AHs), montelukast, danazol, H<sub>2</sub>-antihistamines (H<sub>2</sub>AHs), pentoxifylline, doxepin and tranexamic acid were the most ineffective drugs with <30% patients showing improvement or remission of their UV (Figure 1, Suppl. Tables 3 and 5). H<sub>1</sub>AHs were the most frequently used drugs (107 studies, 294 patients). They were effective in 11 NUV patients, 9 HUV patients and only in one HUVS patient. In the last case, administration of hydroxyzine three times a day produced only slight improvement of skin lesions. Other drugs were evaluated in ≤10 studies and <50 patients. None of the patients benefited during or after the treatment with danazol, H<sub>2</sub>AHs and tranexamic acid.

*Does the treatment of underlying disease lead to UV remission?*

Our findings indicate that UV can be caused by drugs, malignancy and infections and that their withdrawal and cure, respectively, can lead to UV resolution. For example, Kulthanan et al. reported that drugs, most commonly NSAIDs, elicit UV in 7.8% of UV patients.<sup>12</sup> Drug reactions usually occurred in adult patients with acute NUV within 3-10 days after administration of the drug and remission of UV was seen within a month after the drug was discontinued.<sup>7, 12</sup> However, in some cases, UV appeared after a long period of drug intake. For instance, telmisartan-induced UV developed in a patient with hypertension after a year of infrequent ingestion of the drug when he probably started taking the drug more frequently. Re-challenge with a suspected drug confirmed the diagnosis.<sup>40</sup> Therapy with corticosteroids and/or antihistamines was often required to control the symptoms of drug-induced UV.

At least 25-50% of UV patients reportedly have an underlying systemic disease. Solid organ tumors and/or hematologic abnormalities were observed in 4.4-19% of UV patients in our review and other studies, predominantly in adult patients with chronic UV.<sup>7, 12, 25</sup> Malignancy-induced UV had a shorter duration than idiopathic UV.<sup>12</sup> The UV cases listed in Suppl. Table 2 fulfill the two essential criteria for "cutaneous paraneoplastic syndromes":<sup>41</sup> (1) UV reportedly developed after the onset of neoplasm but preceded the diagnosis of malignancy from 3 weeks to several years; and (2) removal of the malignant tumor with chemotherapy, surgical and/or radiation therapy resulted in resolution of UV and its reappearance, if malignancy relapsed.<sup>12, 42-44</sup> Importantly, neoplasms were found primarily due to investigations made because of UV. For example, remission of vasculitis was seen after nephrectomy due to discovery of asymptomatic carcinoma of kidney.<sup>45</sup>

Notably, in some cases, chemotherapy may nonspecifically suppress the symptoms of UV<sup>41</sup> indicating that UV can be a concomitant disease rather than part of a cutaneous paraneoplastic syndrome. Bachmeyer et al. reported UV in 10 (10%) of 95 adult patients with hematologic malignancies.<sup>46</sup> However, they did not find a parallel evolution between both diseases.

Infectious diseases were implicated in the development of UV in 10.2-12.5% cases,<sup>7, 12</sup> including upper respiratory infection, urinary tract infection, rhinosinal aspergillosis, HIV, Lyme disease, parasitic infections and hepatitis A, B and C. HCV-infection, the most common cause of cryoglobulinemia,<sup>47</sup> was diagnosed in 3% of UV patients in our review (1.3-4.3% in other studies<sup>7, 12</sup>), and all but one patient had chronic UV. Cryoglobulinemia is defined by the presence of circulating immunoglobulins, cryoglobulins, which precipitate at temperatures lower than 37°C and form immune complexes affecting small vessels in the skin (cryoglobulinemic vasculitis), kidneys,

peripheral nerves and other organs.<sup>48</sup> Interestingly, HCV has been found together with IgM and IgG in skin lesions of some patients with cutaneous vasculitis.<sup>49</sup> Dupin and coworkers reported urticarial rash in 9% (3/35) of HCV-positive and cryoglobulin-positive patients and in 4% (1/27) of HCV-negative and cryoglobulin-positive patients.<sup>50</sup> Treatment of chronic HCV-infection with interferons and/or antiviral drugs even in a patient with non-active hepatitis<sup>51</sup> and in a patient who did not respond to immunosuppressive treatment<sup>52</sup> led to clearing of UV within 10 days to several weeks and, in some cases, to negative HCV-RNA and cryoglobulins within 1-6 months from the beginning of therapy.<sup>51, 53, 54</sup>

Of 174 UV patients with an underlying systemic disease, 35% had SLE (2-54% in other studies<sup>7, 11, 12</sup>). Most of these patients had HUV/HUVS, which is in line with other studies.<sup>7, 8, 12, 18, 25, 55</sup> Gilliam and Sontheimer classified UV as histologically non-specific lesions of SLE.<sup>56</sup> This implies that UV is related to the underlying SLE, can reflect active disease course and systemic involvement, but can also present in other autoimmune disorders. For example, the occurrence of UV was associated with clinically active SLE in all but one patient in the series reported by Provost et al.<sup>57</sup> Asherson and coauthors described 13 patients with SLE and UV developed at various times during the SLE course.<sup>26</sup> All these patients required moderate-to-high doses of oral corticosteroids and different immunosuppressive agents to control their SLE and UV.

Overall, the existing evidence indicates the need for screening patients with chronic UV for underlying disorders.

#### *What drugs are used for the treatment of UV patients and how effective are they?*

CS are the most frequently administered drugs in UV. Their use has several advantages and disadvantages. Firstly, CS alone or in combination with other drugs were the most effective treatment in all types of UV. They induced improvement or remission of skin symptoms of UV in more than  $\frac{3}{4}$  of UV patients. Secondly, CS were shown to decrease joint, ocular, pulmonary and gastrointestinal symptoms as well as levels of inflammation markers and increase levels of complement components.<sup>13, 58, 59</sup> Thirdly, the speed of action of CS was rapid, usually from one to several days. Finally, CS are widely available and inexpensive.

On the other hand, the long-term administration of CS leads to dose-dependent adverse effects including but not limited to acne, weight gain, glaucoma, high blood pressure and sugar, increased risk of infections, thin skin and bruising, and osteoporosis.<sup>60</sup> In some cases, low doses of prednisolone were ineffective.<sup>23, 61</sup> Moreover, the tapering of prednisolone often leads to relapse of the disease.<sup>55, 58</sup> Thus, the benefits and risks of CS should be weighed when choosing this medication for the treatment of UV, and there is need for safer treatment modalities.

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Biologicals can be used to treat UV even though they have not yet been approved for this. Our systematic review shows that almost all biologicals used were effective in  $\geq 75\%$  UV patients, but the small number of patients treated so far speaks in favor of future research.

Omalizumab, a humanized anti-IgE monoclonal antibody, is a highly effective and safe therapy for chronic urticaria.<sup>62, 63</sup> Omalizumab may be effective in UV through its reduction of IgE and action on cellular activation mechanisms.<sup>64</sup> UV patients might have IgE autoantibodies that have been described in SLE and chronic urticaria.<sup>65</sup> In several case reports, patients experienced an improvement or remission of their UV after treatment with omalizumab without serious adverse effects (Suppl. Tables 5, 6). For example, omalizumab was effective in HUVS patients,<sup>66, 67</sup> in a UV patient with Churg-Strauss syndrome<sup>68</sup> and in patients, who did not improve on previous treatment with antihistamines, CS and/or other immunosuppressive drugs,<sup>67, 68</sup> and allowed to taper the dose of CS.<sup>67, 68</sup>

Anakinra, an IL-1 receptor antagonist, and canakinumab, a long-acting fully humanized monoclonal anti-IL-1 $\beta$  antibody, are highly effective for the treatment of IL-1-associated autoinflammatory syndromes, e.g. CAPS and Schnitzler syndrome. IL-1 was also suggested to play a role in leukocytoclastic vasculitis.<sup>69</sup> In a prospective study, canakinumab improved skin symptoms, joint pain, and general symptoms as well as quality of life, inflammation markers and cytokine levels of IL-1Ra and IL-6 in 10 UV patients.<sup>33</sup> However, canakinumab did not completely abrogate the signs and symptoms of UV suggesting that IL-1 is not the only driving mediator of UV. No serious AEs were reported during canakinumab therapy. Anakinra was effective for UV in two of three case reports.<sup>70-72</sup>

Pro-inflammatory cytokines, TNF- $\alpha$ , TNF-like weak inducer of apoptosis<sup>69, 73</sup> and IL-6,<sup>33, 55</sup> were reported to be increased in patients with leukocytoclastic vasculitis including UV. Anti-TNF agents, etanercept and infliximab, were effective in three patients (Suppl. Tables 5, 6). For example, addition of etanercept to CS in a 2.5-year-old girl with HUVS resulted in disappearance of weakness, morning stiffness and dramatically improved skin lesions and conjunctivitis.<sup>74</sup> Of note, etanercept has been described as a cause of leukocytoclastic vasculitis per se.<sup>75</sup> Tocilizumab, a humanized monoclonal anti-IL-6R antibody, was effective for skin and systemic symptoms in patients with UV and undifferentiated autoinflammatory disorder<sup>71</sup> or SLE.<sup>55</sup>

Lastly, rituximab, an anti-CD20 monoclonal antibody, was effective in NUV (n=2) and HUV/HUVS (n=3) patients.<sup>61, 76</sup> The treatment resulted in fast (usually after the first infusion) and complete remission of cutaneous manifestations of UV, some of the systemic symptoms, and it allowed for tapering the dose of prednisolone. Central line sepsis, thrombosis of retinal artery and panniculitis were noted during treatment with rituximab.<sup>76, 77</sup>

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In many cases, immunosuppressive and immunomodulatory drugs allowed to taper the doses of CS and improved skin and systemic symptoms, laboratory parameters and overall efficacy of therapy (Suppl. Tables 4, 6). For example, six courses of intravenous cyclophosphamide in combination with prednisolone in a HUV patient with cardiac valve involvement improved the general condition, skin, joint and eye symptoms remarkably, with normalization of inflammatory and complement levels.<sup>78</sup> However, none of these agents are approved for the treatment of UV. Moreover, several of them, e.g. colchicine and omalizumab, are unavailable in some countries and/or costs are high.

The adverse effects of some drugs limit their usefulness for the treatment of UV. For instance, several adverse events were described for the following drugs during treatment of UV (Suppl. Tables 5 and 6): dapsone (hypersensitivity syndrome, anemia), methotrexate (hair thinning, fatigue), colchicine (dysphagia, diarrhea, transient numbness of hand), cyclophosphamide (candida stomatitis, hypertension).

In contrast to chronic urticaria,<sup>63</sup> oral H<sub>1</sub>AHs were effective only in 24% of UV patients. Because of their safety profile, the use of H<sub>1</sub>AHs might be considered for symptomatic relief of itch and in patients without systemic complains especially in pediatric population.<sup>14, 15, 25, 37</sup> Combination of second generation H<sub>1</sub>AHs with CS may increase the efficacy of the therapy.<sup>14</sup>

### *Limitations*

There is considerable heterogeneity in the patient demographics among the studies. Patients' age and gender, duration of UV, concomitant diseases and extracutaneous symptoms may be important when examining the efficacy of the treatment. Most articles included are case reports, case series or small retrospective and descriptive studies uncontrolled for referral bias, including abstracts from conferences and congresses. In some reports, patient (e.g. age, gender) and disease (e.g. duration, type of UV) characteristics were not described. Some HUV patients could have underdiagnosed HUVS, the diagnosis of which was not obvious at the time of the study. Many studies indicated the response to treatment without clarifying the doses of drug, the treatment duration, measurement of treatment efficacy, the speed of effect and/or follow-up period. In many cases combinations of drugs were used.

The diagnosis of UV can be challenging from a histological point of view, and some authors differed in their definition of UV.<sup>34, 79, 80</sup> For example, Lee and coworkers reported 22 patients with clinical features of UV, with the majority of patients showing a lymphocytic predominant vasculitis with eosinophils.<sup>34</sup> On the other hand, Guitart proposed that only disease with histologic criteria of leukocytoclastic vasculitis can be termed as UV.<sup>79</sup>

Several articles have reported an urticarial rash with neutrophilic infiltrate lasting 48-72 hours in patients with autoimmune connective tissue disorders and autoinflammatory diseases. This rash was defined as “neutrophilic urticaria”, “neutrophilic urticarial dermatosis” and “autoimmunity-related neutrophilic dermatitis”.<sup>81-83</sup> Neutrophilic urticaria was characterized as the presence of wheals with a mixed infiltrate of neutrophils and, to a lesser degree, eosinophils but without leukocytoclasia, fibrinoid necrosis and hemorrhage.<sup>83</sup> Saeb-Lima and coauthors suggested that autoimmunity-related neutrophilic dermatitis differs from UV. They described the histologic findings as “a neutrophilic dermal infiltrate with leukocytoclasia, vascular alteration along the dermal-epidermal junction, and no vasculitis”.<sup>81</sup> However, other reports did not include fibrinoid necrosis as a major criterion for the diagnosis of vasculitis. This indicates an overlap between neutrophilic urticaria/dermatosis and neutrophilic UV. Several studies considered these disorders as polar diseases within the same spectrum and suggested that a continuum exists in the histopathologic changes.<sup>31, 35, 81</sup>

Importantly, neutrophilic urticarial dermatosis strongly points to possible underlying systemic diseases, e.g. rheumatological disease or Schnitzler syndrome.<sup>84</sup> Despite the fact that urticarial rash in some patients with Schnitzler syndrome has been reported as leukocytoclastic vasculitis<sup>85, 86</sup>, we did not include these patients because Schnitzler syndrome is a well-characterized separate entity.

Direct immunofluorescence (DIF) was done only in some patients. Moreover, DIF was negative in some patients with biopsy findings of UV.<sup>87</sup> Vice versa, DIF was positive (IgM in the vessel lumen and focal deposition of granular C3 in the vessel walls<sup>88</sup>) in UV cases with mixed perivascular infiltrate, extravasation of erythrocytes but without fibrinoid necrosis of vessel walls.

#### *Unmet needs and conclusions*

In summary, none of the drugs reported to be effective in the treatment of UV patients has yet been approved for UV, and management recommendations are based mostly on case reports and retrospective studies. We identified several needs for further research:

- Agreement on the proper nosology and classification of UV based on the clinical picture and histology findings is crucial. There is a high need for the development of clinical and histological diagnostic criteria of UV.
- What are the prognostic factors of UV duration and severity? Do some subpopulations of healthy individuals and patients with other diseases have a higher probability of being affected by UV?

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- Disease-specific instruments are needed to measure disease activity and its changes in UV.
  - Further studies are needed to evaluate potentially safe and effective drugs for the treatment of UV, e.g. omalizumab. This should include prospective randomized double-blind, placebo-controlled trials with parallel-group or cross-over design depending on the treatment investigated, using validated clinical outcome, as well as a registry for real-life data on UV patient characteristics, the course of the disease, underlying causes, comorbidities, and treatment responses. Both, prospective trials and a UV registry would benefit from validated histological criteria of UV as well as PROs to measure disease activity and changes of disease activity in response to treatment.
  - Can clinical characteristics of UV, serum or histological markers, be predictors of response to treatment?
  - A stepwise algorithm of treatment of UV should be developed for use in everyday clinical practice.

#### **What do we know?**

- Urticarial vasculitis (UV) is a difficult-to-treat condition characterized by urticarial rashes with lesions of >24 h duration, histopathologic findings of leukocytoclastic vasculitis and, frequently, extracutaneous symptoms.
- UV is usually idiopathic, but can be associated with drugs (primarily acute UV), malignancy, autoimmunity, and infections (primarily chronic UV), in which case UV usually resolves with their withdrawal or cure.
- Corticosteroids are effective for the treatment of skin and extracutaneous symptoms in most patients.

#### **What is still unknown?**

- The proper nosology, classification, clinical and histological criteria of UV.
- Prognostic factors and biomarkers of UV duration, severity and response to treatment.
- Potentially safe and effective drugs for the treatment of UV.

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## Figure legends

**Figure 1. Responses to various drugs in urticarial vasculitis.** In many cases, IVIG, methotrexate, cyclosporine, dapsone, mycophenolate mofetil, colchicine, hydroxychloroquine and cyclophosphamide were used in combination with corticosteroids. IVIG: intravenous immunoglobulins; NSAIDs: nonsteroidal antiinflammatory drugs; AHs: antihistamines.

**Table 1. UV patients' demographics**

| Characteristics                                         |                       | Data                      |
|---------------------------------------------------------|-----------------------|---------------------------|
| Sex, female, % (n)                                      |                       | 66 (452/686)              |
| Age, range in years                                     |                       | 0.5-86 <sup>1</sup>       |
| Duration, % (n)                                         | Acute UV (<6 weeks)   | 5 (34/711)                |
|                                                         | Chronic UV (≥6 weeks) | 95 (677/711)              |
| Extracutaneous manifestations, % (n)                    |                       | 83 (398/479) <sup>2</sup> |
| Type of UV based on complement levels, % (n)            | NUV                   | 49 (285/585)              |
|                                                         | HUV                   | 39 (227/585)              |
|                                                         | HUVS                  | 12 (73/585)               |
| Type of UV based on biopsy findings, % (n) <sup>3</sup> | Leukocytoclastic UV   | 96 (228/237)              |
|                                                         | Lymphocytic UV        | 4 (9/237)                 |

<sup>1</sup>more than 80% of patients were older than 17 years; <sup>2</sup>mostly joint, ocular and gastrointestinal symptoms; <sup>3</sup>infiltrates consisting of neutrophils, lymphocytes, eosinophils or polymorphonuclear leukocytes were seen in 93, 43, 47 and 10 patients, respectively. Among these patients, at least 44 patients had a mixed infiltrate; NUV: normocomplementemic UV; HUV: hypocomplementemic urticarial vasculitis; HUVS: hypocomplementemic urticarial vasculitis syndrome.

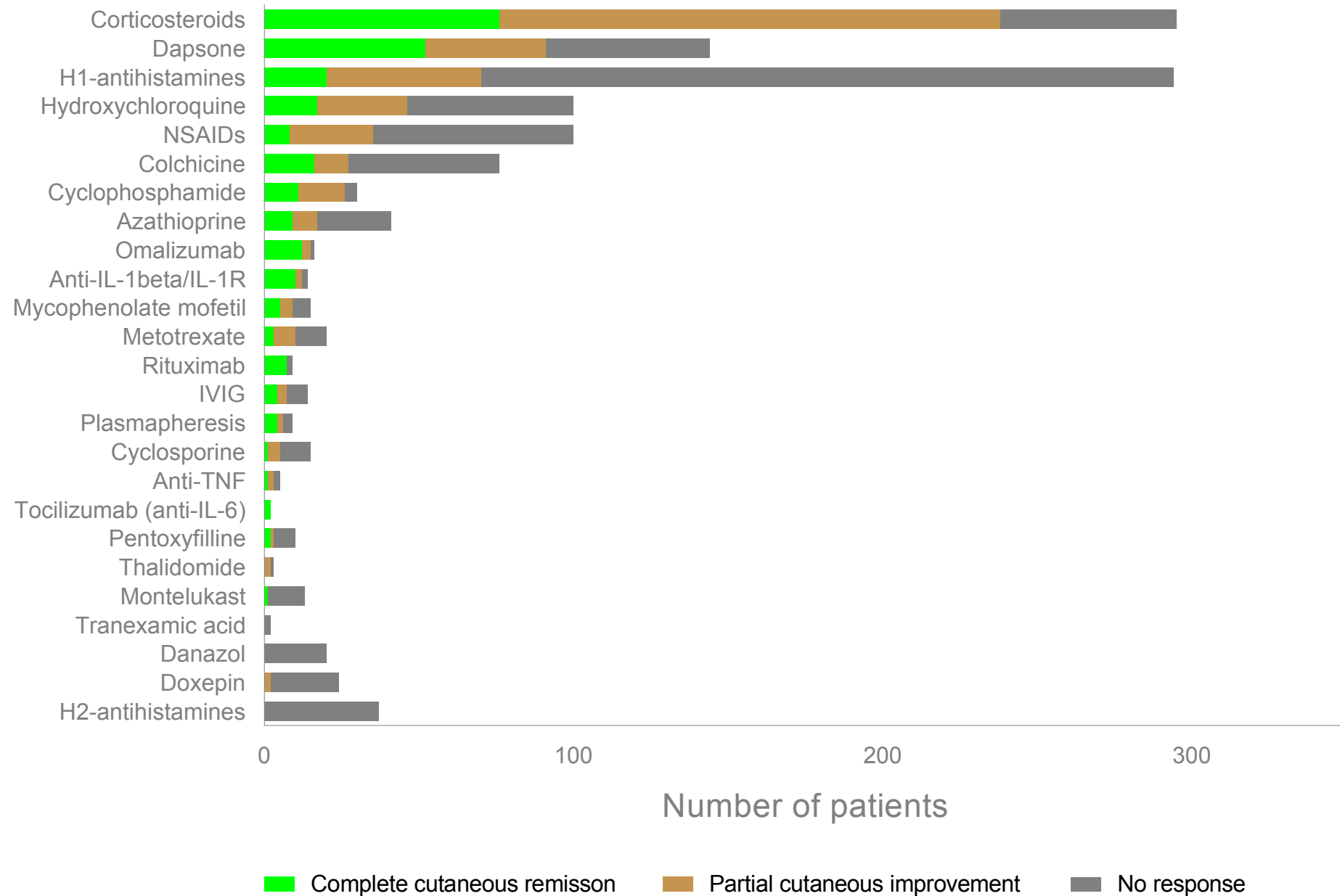
Table 2. Comorbid diseases in UV patients

| Comorbid diseases                                               |                                      | Number of UV patients   |
|-----------------------------------------------------------------|--------------------------------------|-------------------------|
| <b>Any comorbid diseases<sup>1</sup>, % (n)</b>                 |                                      | 31 (174/556)            |
| <b>Autoimmune diseases, % (n)</b>                               | <i>Any</i>                           | 17 (93/556)             |
|                                                                 | <i>SLE</i>                           | 11 (61/556)             |
|                                                                 | <i>AITD</i>                          | 2 (9/556)               |
|                                                                 | <i>Other</i>                         | 4 (23/556)              |
| <b>Malignancy, % (n)</b>                                        | <i>Any</i>                           | 7 (38/556)              |
|                                                                 | <i>Hematologic</i>                   | 3.5 (19/556)            |
|                                                                 | <i>Solid tumors</i>                  | 3.5 (19/556)            |
| <b>Infection, % (n)</b>                                         | <i>Any</i>                           | 6 (31/556)              |
|                                                                 | <i>Viral</i>                         | 4 (21/556) <sup>2</sup> |
|                                                                 | <i>Bacterial</i>                     | 1 (7/556)               |
|                                                                 | <i>Parasitic</i>                     | <1 (2/556)              |
| <b>Mixed cryoglobulinemia, % (n)</b>                            | <i>Any</i>                           | 2 (10/556)              |
|                                                                 | <i>Associated with HCV infection</i> | 1 (7/556)               |
| <b>Monoclonal gammopathy, % (n)</b>                             |                                      | 1 (6/556)               |
| <b>Inflammatory bowel diseases, % (n)</b>                       |                                      | 1 (6/556)               |
| <b>Other diseases, % (n)</b>                                    |                                      | 4 (20/556)              |
| <b>Two or more comorbid diseases in the same patient, % (n)</b> |                                      | 4 (22/556)              |

<sup>1</sup>of 789 patients, information on the presence or absence of comorbidities was available for 556 patients and not available for 233 patients; <sup>2</sup>chronic HCV infection was diagnosed in 15 cases; SLE: systemic lupus erythematosus; AITD: autoimmune thyroid disease

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# Responses to various drugs in urticarial vasculitis



**Suppl. Table 1. PICOS Worksheet and Search Strategy**

| <b>Parameter</b> | <b>Inclusion criteria</b>                                                                                                                                     | <b>Exclusion criteria</b>                                                                                            |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| Patients         | Any age and any gender with different forms of urticarial vasculitis (NUV, HUV, HUVS)                                                                         | Urticaria patients, patients with Schnitzler syndrome, patients without clinical and/or histological diagnosis of UV |
| Intervention     | Treatment with various drugs                                                                                                                                  | –                                                                                                                    |
| Comparator       | Placebo and various drugs, when available                                                                                                                     | –                                                                                                                    |
| Outcomes         | Efficacy of various drugs for treatment of UV skin and systemic symptoms                                                                                      | –                                                                                                                    |
| Study Design     | Randomized and non-randomized controlled trials, retrospective, prospective or concurrent cohort studies, cross-sectional studies, case reports (≥1 patients) | Basic research studies, reviews                                                                                      |

Suppl. Table 2. Does the treatment of underlying disease or withdrawal of drugs lead to UV remission?

| Author, year [Ref]            | Age of patients, y | Type of UV | Duration of UV | Drug, underlying disease or other cause | Specific treatment                           | Efficacy of treatment |                        |
|-------------------------------|--------------------|------------|----------------|-----------------------------------------|----------------------------------------------|-----------------------|------------------------|
|                               |                    |            |                |                                         |                                              | Underlying disease    | UV                     |
| DRUGS AND OCCUPATIONAL AGENTS |                    |            |                |                                         |                                              |                       |                        |
| Polat 2017 <sup>1</sup>       | 77                 | –          | A              | Deferasirox                             | Withdrawal of drug; CS, AHs                  | –                     | Remission              |
| Zhu 2016 <sup>2</sup>         | 50                 | NUV        | C              | Metformin                               | Withdrawal of drug; CS                       | –                     | Remission              |
| Koregol 2015 <sup>3</sup>     | 71                 | NUV        | A              | Enalapril                               | Withdrawal of drug; CS                       | –                     | Remission              |
| Mahajan 2015 <sup>4</sup>     | 53                 | NUV        | A              | Telmisartan                             | Withdrawal of drug; CS, AHs                  | –                     | Remission              |
| Ojeda 2015 <sup>5</sup>       | 35                 | NUV        | A              | Diet pills                              | Withdrawal of drug; CS, AHs                  | –                     | Remission              |
| Mangal 2014 <sup>6</sup>      | 11                 | NUV        | A              | Levetiracetam                           | Withdrawal of drug; CS, AHs                  | –                     | Remission              |
| Bock 2014 <sup>7</sup>        | 69                 | –          | A              | Anastrozole                             | Withdrawal of drug; CS                       | –                     | Remission              |
| Hughes 2010 <sup>8</sup>      | 21                 | NUV        | A              | H1N1 vaccination                        | No revaccination; AHs                        | –                     | Remission              |
| Bellini 2010 <sup>9</sup>     | 79                 | –          | A              | Simvastatin                             | Withdrawal of drug; CS                       | –                     | Remission              |
| Cicek 2008 <sup>10</sup>      | 48                 | HUV        | A              | Glatiramer acetate                      | Withdrawal of drug; CS                       | –                     | Remission              |
| Goulao 2008 <sup>11</sup>     | 61                 | –          | A              | Infliximab                              | Withdrawal of drug; CS                       | –                     | Remission              |
| Pellizzari 2007 <sup>12</sup> | 40                 | NUV        | A              | Formaldehyde                            | Elimination of exposure to formaldehyde; CS  | –                     | Remission              |
| Lopes 2006 <sup>13</sup>      | 68                 | NUV        | A              | Pemetrexed                              | Withdrawal of drug; CS                       | –                     | Remission              |
| Feiza 2005 <sup>14</sup>      | 30                 | –          | C              | Sulfamethoxazole-trimethoprim           | Withdrawal of drug; CS                       | –                     | Improvement            |
| Loche 1997 <sup>15</sup>      | –                  | –          | A              | Phenobarbital quinidine                 | Withdrawal of drug                           | –                     | Remission              |
| Papadavid 1996 <sup>16</sup>  | 39                 | HUV        | A              | Dexfenfluramine                         | Withdrawal of drug; CS                       | –                     | Improvement            |
| Roger 1995 <sup>17</sup>      | 49                 | –          | A              | Fluoxetine                              | Withdrawal of drug                           | –                     | Remission              |
| Mosovich 1991 <sup>18</sup>   | 29                 | –          | A              | Oral contraceptive                      | Withdrawal of drug                           | –                     | Improvement            |
| Mitchell 1983 <sup>19</sup>   | 63                 | –          | A              | Cimetidine                              | Withdrawal of drug; CS                       | –                     | Remission              |
| MALIGNANCY                    |                    |            |                |                                         |                                              |                       |                        |
| Kassim 2015 <sup>20</sup>     | 72                 | NUV        | C              | Chronic lymphocytic leukemia            | Chemotherapy                                 | Improvement           | Remission              |
| Alizadeh 2007 <sup>21</sup>   | 23                 | HUV        | C              | Castleman's disease <sup>4</sup>        | Splenectomy                                  | Improvement           | Improvement            |
| Eilertsen 2006 <sup>22</sup>  | 36                 | HUV        | C              | Erythroleukemia                         | Chemotherapy+transplantation of stem cells   | Remission             | Remission              |
| Zhang 2004 <sup>23</sup>      | 79                 | NUV        | C              | Multiple myeloma                        | Melphalan or endoxan + predonine             | Improvement           | Remission              |
| Wang 2003 <sup>24</sup>       | 37                 | –          | C              | Nasopharyngeal carcinoma                | CS, chemotherapy and radiation therapy       | Cure                  | Remission              |
| Di Stefano 2003 <sup>25</sup> | 42                 | NUV        | C              | Cystic teratoma                         | Surgical resection                           | Cure                  | Remission              |
| Ducarme 2003 <sup>26</sup>    | 37                 | –          | C              | Renal carcinoma                         | Specific treatment                           | Cure                  | Remission              |
| Farell 1996 <sup>27</sup>     | 77                 | NUV        | C              | Polycythemia rubra vera                 | Phlebotomy                                   | Improvement           | Remission              |
| Sprossmann 1994 <sup>28</sup> | 30                 | –          | C              | Malignant testicular teratoma           | Oncological and surgical therapy of teratoma | Improvement           | Improvement            |
| Lacour 1993 <sup>29</sup>     | 75                 | NUV        | A              | Renal carcinoma                         | Nephrectomy                                  | Cure                  | Remission              |
| Carsuzaa 1992 <sup>30</sup>   | 73                 | –          | C              | Renal carcinoma                         | Surgical resection                           | Cure                  | Remission              |
| HEPATITIS                     |                    |            |                |                                         |                                              |                       |                        |
| Foschi 2010 <sup>31</sup>     | 77                 | NUV        | C              | Chronic hepatitis C                     | PEG-IFN α-2a, HLI, ribavirin                 | Improvement           | Remission <sup>2</sup> |
| Husa 2005 <sup>32</sup>       | –                  | –          | C              | Chronic hepatitis C                     | IFN α-2a and ribavirin                       | Cure                  | Remission              |
| Svobodova 2005 <sup>33</sup>  | 43                 | –          | C              | Chronic hepatitis C                     | Antiviral treatment                          | –                     | Remission              |
| Kelkar 2002 <sup>34</sup>     | 29                 | HUV        | C              | Chronic hepatitis C                     | Doxepin, IFN-α, ribavirin                    | –                     | Improvement            |
| Hamid 1998 <sup>35</sup>      | 37-52              | HUV        | C              | Chronic hepatitis C                     | IFN α-2β                                     | Cure                  | Remission              |

|                                       |       |     |   |                                             |                                           |             |                        |
|---------------------------------------|-------|-----|---|---------------------------------------------|-------------------------------------------|-------------|------------------------|
|                                       |       | –   | C | Chronic hepatitis C                         | IFN α-2β                                  | Improvement | Remission <sup>1</sup> |
| Matteson 1996 <sup>36</sup>           | 68    | –   | C | After acute hepatitis A                     | IFN α-2a                                  | –           | Remission              |
| Karlsberg 1995 <sup>37</sup>          | 31    | –   | C | Chronic hepatitis C                         | IFN-α                                     | –           | Remission              |
| Popp 1981 <sup>38</sup>               | 22-32 | HUV | A | Acute hepatitis B                           | No specific treatment                     | Cure        | Remission <sup>3</sup> |
|                                       |       | HUV | A | Acute hepatitis B                           | No specific treatment                     | Cure        | Remission <sup>3</sup> |
|                                       |       | –   | A | Acute hepatitis B                           | No specific treatment                     | Cure        | Remission <sup>3</sup> |
| OTHER INFECTIONS                      |       |     |   |                                             |                                           |             |                        |
| Diplomatico 2017 <sup>39</sup>        | 17    | NUV | C | <i>Mycoplasma pneumoniae</i> infection      | Clarithromycin                            | –           | Remission              |
| Shaigany 2015 <sup>40</sup>           | 36    | NUV | C | Neurocysticercosis                          | Neurosurgical removal of cyst+albendazole | Cure        | Remission              |
| Benson 2014 <sup>41</sup>             | 32    | –   | A | <i>Mycobacterium tuberculosis</i> infection | Anti-tuberculosis therapy                 | –           | Remission              |
| Jover 2003 <sup>42</sup>              | 51    | NUV | C | <i>Mycoplasma pneumoniae</i> infection      | Ceftriaxone, clarithromycin, doxycycline  | –           | Remission              |
| Purello-D'Ambrosio 1999 <sup>43</sup> | 32    | HUV | C | <i>Trichomonas vaginalis</i> infection      | Metronidazole                             | Cure        | Remission              |
| Misery 1993 <sup>44</sup>             | 21    | HUV | C | BCG-vaccine-induced UV                      | Rifampicin+isoniazid                      | –           | Remission              |
| Rakita 1993 <sup>45</sup>             | 38    | –   | C | Filariasis                                  | Diethylcarbamazine                        | Cure        | Remission              |
| Olson 1990 <sup>46</sup>              | 4     | NUV | C | Lyme disease                                | Penicillin                                | –           | Remission              |
| OTHER POSSIBLE CAUSES                 |       |     |   |                                             |                                           |             |                        |
| Sengul Emeksiz 2016 <sup>47</sup>     | 13    | –   | A | Autoimmune thyroiditis                      | Levothyroxine+CS+AHs                      | –           | Remission              |
| Hofbauer 1999 <sup>48</sup>           | 24    | NUV | A | Cocaine use                                 | No cocaine use; CS; antihistamines        | –           | Remission              |
| Wüthrich 1993 <sup>49</sup>           | 47    | NUV | C | Disufite                                    | Avoidance of sulfited foods and drugs+CS  | –           | Remission              |
| Granier 1987 <sup>50</sup>            | –     | NUV | C | Autoimmune throiditis                       | Levothyroxine                             | –           | Remission              |

<sup>1</sup>In one patient, UV recurred upon discontinuation of treatment and HCV RNA was again detectable; <sup>2</sup>skin biopsy was not done but the signs and symptoms were suggestive of UV; <sup>3</sup>after hepatitis cure; <sup>4</sup>Castleman's disease is considered to be not malignant but has the malignant potential; CS: corticosteroids; IFN: interferon; HLI: human leucocyte interferon- $\alpha$ ; AHs: antihistamines; A: acute UV (<6 weeks); C: chronic UV ( $\geq$ 6 weeks);

**Suppl. Table 3. Summary on the efficacy of drugs in the treatment of skin symptoms of urticarial vasculitis**

| Drugs                                         | % (n/total), studies where drug was effective at least in 1 UV patient | % (n), UV patients treated |                    |                     |                 |               |
|-----------------------------------------------|------------------------------------------------------------------------|----------------------------|--------------------|---------------------|-----------------|---------------|
|                                               |                                                                        | Total, n                   | Complete remission | Partial improvement | Total benefited | Not effective |
| CS monotherapy                                | 81 (117/144)                                                           | 295                        | 26 (76)            | 55 (162)            | 81 (238)        | 19 (57)       |
| CS±H <sub>1</sub> AHs                         | 84 (139/165)                                                           | 346                        | 30 (103)           | 51 (177)            | 81 (280)        | 19 (66)       |
| Omalizumab                                    | 92 (12/13)                                                             | 16                         | 75 (12)            | 19 (3)              | 94 (15)         | 6 (1)         |
| Cyclophosphamide±CS                           | 87 (20/23)                                                             | 30                         | 37 (11)            | 50 (15)             | 87 (26)         | 13 (4)        |
| Plasmapheresis±CS                             | 62 (5/8)                                                               | 9                          | 44 (4)             | 23 (2)              | 67 (6)          | 33 (3)        |
| Anti-TNF (etanercept or infliximab) ±CS       | 60 (3/5)                                                               | 5                          | 20 (1)             | 40 (2)              | 60 (3)          | 40 (2)        |
| Anti-IL-1β/IL-1R (anakinra or canakinumab)±CS | 60 (3/5)                                                               | 14                         | 15 (2)             | 71 (10)             | 86 (12)         | 14 (2)        |
| Rituximab±CS                                  | 78 (7/9)                                                               | 9                          | 78 (7)             | 0 (0)               | 78 (7)          | 22 (2)        |
| Anti-IL6 (tocilizumab)                        | 100 (2/2)                                                              | 2                          | 100 (2)            | 0 (0)               | 100 (2)         | 0 (2)         |
| HCQ±CS                                        | 35 (15/43)                                                             | 100                        | 17 (17)            | 29 (29)             | 46 (46)         | 54 (54)       |
| HCQ monotherapy                               | 23 (7/31)                                                              | 97                         | 10 (10)            | 29 (28)             | 39 (38)         | 61 (59)       |
| NSAIDs monotherapy                            | 34 (10/29)                                                             | 100                        | 8 (8)              | 27 (27)             | 35 (35)         | 65 (65)       |
| CLH±CS                                        | 49 (20/41)                                                             | 76                         | 21 (16)            | 15 (11)             | 36 (27)         | 64 (49)       |
| Dapsone±CS                                    | 64 (39/61)                                                             | 144                        | 36 (52)            | 27 (39)             | 63 (91)         | 37 (53)       |
| MMF±CS                                        | 60 (9/15)                                                              | 15                         | 33 (5)             | 27 (4)              | 60 (9)          | 40 (6)        |
| CYC±CS                                        | 38 (5/13)                                                              | 15                         | 7 (1)              | 27 (4)              | 34 (5)          | 66 (10)       |
| AZA±CS                                        | 51 (17/33)                                                             | 41                         | 22 (9)             | 19 (8)              | 41 (17)         | 59 (24)       |
| MTX±CS                                        | 47 (8/17)                                                              | 20                         | 15 (3)             | 35 (7)              | 50 (10)         | 50 (10)       |
| IVIG±other drugs                              | 54 (7/13)                                                              | 14                         | 29 (4)             | 21 (3)              | 50 (7)          | 50 (7)        |
| Thalidomide                                   | 50 (1/2)                                                               | 3                          | 0 (0)              | 67 (2)              | 67 (2)          | 33 (1)        |
| Antibiotics                                   | 42 (5/12)                                                              | 12                         | 42 (5)             | 0 (0)               | 42 (5)          | 58 (7)        |
| Antihelmintics                                | 67 (2/3)                                                               | 3                          | 67 (2)             | 0 (0)               | 67 (2)          | 33 (1)        |
| Danazol                                       | 0 (0/3)                                                                | 20                         | 0 (0)              | 0 (0)               | 0 (0)           | 100 (20)      |
| H <sub>1</sub> AHs monotherapy                | 17 (18/107)                                                            | 294                        | 7 (20)             | 17 (50)             | 24 (70)         | 76 (224)      |
| H <sub>2</sub> AHs                            | 0 (0/16)                                                               | 37                         | 0 (0)              | 0 (0)               | 0 (0)           | 100 (37)      |
| Montelukast                                   | 11 (1/9)                                                               | 13                         | 8 (1)              | 0 (0)               | 8 (1)           | 92 (12)       |
| Pentoxifylline ± other drugs                  | 43 (3/7)                                                               | 10                         | 20 (2)             | 10 (1)              | 30 (3)          | 70 (7)        |
| Doxepin                                       | 33 (2/6)                                                               | 24                         | 0 (0)              | 8 (2)               | 8 (2)           | 92 (22)       |
| Tranexamic acid                               | 0 (0/2)                                                                | 2                          | 0 (0)              | 0 (0)               | 0 (0)           | 100 (2)       |

CS: corticosteroids; IVIG: intravenous immunoglobulins; CYC: cyclosporine; AZA: azathioprine; MTX: methotrexate; TNF: tumor necrosis factor; MMF: mycophenolate mofetil; HCQ: hydroxychloroquine; CLH: colchicine; AHs: antihistamines

Suppl. Table 4. Summary on the drugs successfully used for the treatment of urticarial vasculitis

| Drugs <sup>1</sup>     | Cases, n | Age  | Initial dose                                |                  | Duration of the treatment | UV group*      | Efficacy       |                           | Efficacy seen within              | Duration of improvement***   | Relapse of the disease after discontinuation of treatment or tapering the dose?*** | Steroid-sparing effect** |
|------------------------|----------|------|---------------------------------------------|------------------|---------------------------|----------------|----------------|---------------------------|-----------------------------------|------------------------------|------------------------------------------------------------------------------------|--------------------------|
|                        |          |      | Range                                       | In most patients |                           |                | Skin symptoms* | Extracutaneous symptoms** |                                   |                              |                                                                                    |                          |
| Corticosteroids        | >71      | A, C | 5-60 mg/d                                   | 40-60 mg/d       | Several months-years      | HUV, HUVS      | CR             | ↓JS, OS, PS, GS, IM, ↑CT  | Rapid-1 month                     | While on treatment           | Yes                                                                                | –                        |
| Dapsone                | 59       | A, C | 25-300 mg/d                                 | 50-100 mg/d      | 5 weeks-2 years           | NUV, HUV, HUVS | CR             | ↓fever, JS, IM, ↑CT       | 1 day-1 month                     | While on treatment (in most) | Yes, no                                                                            | Yes                      |
| Omalizumab             | 15       | A    | 150-300 mg every other week or monthly      | 300 mg monthly   | 6-23 months               | NUV, HUVS      | CR             | ↓GS, ↑CT                  | After first dose-4 months         | While on treatment           | Yes                                                                                | Yes                      |
| Canakinumab            | 10       | A    | 300 mg                                      |                  | Single dose               | NUV            | PI             | ↓JS, GS, IM               | 16 weeks                          | –                            | –                                                                                  | –                        |
| NSAIDs                 | 10       | A    | 25 mg twice daily – 50 mg/ four times daily |                  | 1-21 months               | HUV, NUV       | PI-CR          | ↓JS, GS, PS               | 17 days                           | –                            | Yes                                                                                | –                        |
| CLH                    | 10       | A    | 0.5 mg/d – 0.6 mg three times a day         | 1.0-1.2 mg/d     | 1-30 months               | HUV, NUV       | CR             | ↓JS, GS                   | A few days-a month                | While on treatment           | Yes                                                                                | Yes                      |
| HCQ                    | 7        | A    | 100-400 mg/d                                | 400 mg/d         | 1-2 years                 | HUV, HUVS      | CR             | ↓JS, OS, PS, ↑CT          | 3 months                          | While on treatment           | Yes                                                                                | Yes                      |
| Reserpine <sup>2</sup> | 7        | C    | 0.3-0.4 mg/d                                |                  | 4-8 weeks                 | NUV            | PI-CR          | –                         | 4 days                            | –                            | –                                                                                  | –                        |
| MMF                    | 6        | A    | 1-2 g/d                                     |                  | 15-32 months              | HUV, HUVS      | CR             | ↓JS, OS, ↑CT              | 2-6 months                        | 10 months-2 years            | No                                                                                 | Yes                      |
| Rituximab              | 6        | A    | 375-1000 mg                                 |                  | 4 weeks                   | NUV, HUV, HUVS | CR             | ↓GS, JS, ↑CT              | After 1 injection-1 month         | 4 weeks-30 months            | Yes, no                                                                            | Yes                      |
| IVIG                   | 4        | A, C | 400 mg/kg/d – 2 g/kg/d                      |                  | Several cycles            | HUV, HUVS      | PI-CR          | ↓JS, OS, GS, ↑RF          | After 1 cycle                     | –                            | Yes                                                                                | –                        |
| Cyclophosphamide       | 4        | A    | 15 mg/kg-500 mg every two weeks             |                  | 9 months-16 pulses        | HUV, HUVS      | CR             | ↓JS, OS, GS, IM, ↑CT      | After 6-10 courses                | –                            | –                                                                                  | –                        |
| MTX                    | 3        | A    | 7.5-15.0 mg weekly                          |                  | 3 weeks-6 months          | –              | PI-CR          | –                         | 1-3 months                        | –                            | –                                                                                  | –                        |
| Plasmapheresis         | 2        | A    | Two-three sessions                          |                  | 6 months                  | NUV, HUVS      | CR             | ↓fever, NS, ↑CT           | 1 day after last session          | –                            | –                                                                                  | –                        |
| CYC                    | 2        | A    | 3 mg/kg/d-200 mg/d                          |                  | –                         | HUVS           | PI-CR          | ↓JS                       | 2 months                          | 6 months                     | –                                                                                  | Yes                      |
| AZA                    | 2        | A    | 100-150 mg/d                                |                  | A few weeks               | NUV            | PI-CR          | –                         | A few weeks                       | –                            | –                                                                                  | Yes                      |
| Anakinra               | 2        | A, C | 100 mg/d                                    |                  | 3-13 months               | NUV            | CR             | ↓GS, JS, IM               | Immediate-2 weeks                 | 13 months                    | Yes                                                                                | Yes                      |
| Tocilizumab            | 2        | A, C | 8 mg/kg/month                               |                  | 2 infusions               | HUV            | CR             | ↓fever, JS, PS, GS        | Several days after first infusion | 1.0-2.5 years                | –                                                                                  | Yes                      |
| Infliximab             | 1        | A    | –                                           |                  | >2 years                  | HUVS           | CR             | ↓ OS, PS, IM, ↑CT         | 6 weeks                           | >2.5 years                   | –                                                                                  | Yes                      |
| Etanercept             | 1        | A    | 2 mg twice weekly                           |                  | –                         | –              | PI             | –                         | –                                 | –                            | –                                                                                  | –                        |

A: adult; C: children; CR: complete cutaneous remission; PI: partial cutaneous improvement; HUV: hypocomplementemic urticarial vasculitis; HUVS: hypocomplementemic urticarial vasculitis syndrome; NUV: normocomplementemic urticarial vasculitis; IVIG: intravenous immunoglobulins; CYC: cyclosporine; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil; HCQ: hydroxychloroquine; CLH: colchicine; NSAIDs: nonsteroidal antiinflammatory drugs; ↓/↑: decrease (normalization) or increase of symptoms (parameters); JS: joint symptoms (arthralgia/arthritis); IM: inflammatory markers (e.g. ESR, CRP); CT: complement components; OS: ocular symptoms

(e.g. uveitis); PS: pulmonary symptoms (e.g. cough); GS: gastrointestinal symptoms (e.g. abdominal pain); NS: neurological symptoms; RF: renal function; \*most patients; \*\*seen in  $\geq 1$  patient; \*\*\*during the treatment or after withdrawal of the drug (Suppl. Table 4); <sup>1</sup>many immunosuppressive drugs were used in the combination with CS (Suppl. Table 4); <sup>2</sup>in the combination with antihistamines

Suppl. Table 5. Efficacy of drugs in the treatment of urticarial vasculitis

| First author                 | Year       | Country | Age of patients, y | n, patients treated | Gender         | UV group (n)       | Extracutaneous symptoms (n) | Acute or chronic (< or ≥ 6 weeks, n) | Underlying systemic disease (n)                                     | Biopsy         | Efficacy of drugs regarding urticarial rash (n/total of patients treated) |                                    |                                                                                                                           |                                                   |
|------------------------------|------------|---------|--------------------|---------------------|----------------|--------------------|-----------------------------|--------------------------------------|---------------------------------------------------------------------|----------------|---------------------------------------------------------------------------|------------------------------------|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
|                              |            |         |                    |                     |                |                    |                             |                                      |                                                                     |                | H <sub>1</sub> AHs                                                        | Systemic CS                        | Immunosuppressive drugs                                                                                                   | Biologicals and other drugs                       |
| Polat <sup>1</sup>           | 2017       | Turkey  | 77                 | 1                   | f              | Drug-induced       | No                          | A                                    | Diabetes                                                            | NI, EI, LCV    |                                                                           |                                    |                                                                                                                           | Withdrawal of the drug+CS+H <sub>1</sub> AHs (CR) |
| Al Hermi <sup>51</sup>       | 2017       | Bahrain | 6                  | 1                   | m              | HUVS               | Yes                         | C                                    | No                                                                  | EI             |                                                                           |                                    | CS+AZA (CR)                                                                                                               |                                                   |
| Tanaka <sup>52</sup>         | 2017       | Japan   | 64                 | 1                   | f              | HUVS               | Yes                         | C                                    | No                                                                  | LCV            |                                                                           | PI-CR <sup>ex,1</sup>              |                                                                                                                           |                                                   |
| Reszke <sup>53</sup>         | 2017       | Poland  | 69                 | 1                   | m              | HUV                | No                          | C                                    | Primary myelofibrosis                                               | LI, NI, EI, UV | No <sup>sg</sup>                                                          | CR                                 |                                                                                                                           |                                                   |
| Aurich <sup>54</sup>         | 2017       | Germany | 36                 | 1                   | f              | HUVS               | Yes                         | C                                    | No                                                                  | NI             | No <sup>st,h</sup>                                                        |                                    | MMF+CS (no), CYC+MMF+CS (PI)                                                                                              | MMF+CS+OMA (no),                                  |
| Gheerbrant <sup>55</sup>     | 2017       | France  | 41                 | 1                   | f              | HUVS               | Yes                         | C                                    | No                                                                  | LCV            | No                                                                        |                                    | CS+MMF (PI)                                                                                                               | OMA (PI)                                          |
| Jachiet <sup>56, 57</sup>    | 2017, 2015 | France  | >14                | 57                  | f (42), m (15) | HUV (57)           | Yes (39)                    | C (57)                               | Yes (in 14)                                                         | LCV            | No <sup>st,h</sup> (57/57)                                                | CR <sup>i</sup> (7/32), PI (15/32) | HCQ (CR 7/24, PI 11/24), CLH (CR 2/7, PI 2/7), AZA <sup>i</sup> (CR 1/2, PI 1/2), MMF <sup>i</sup> (PI 1/1), CYC (PI 1/1) | DP (CR 1/1)                                       |
| Nucera <sup>58</sup>         | 2017       | Italy   | 47                 | 1                   | f              | HUVS               | Yes                         | C                                    | No                                                                  | EI             |                                                                           |                                    | H <sub>1</sub> AHs <sup>i</sup> +HCQ+CS (no),                                                                             | OMA (CR)                                          |
| Rolls <sup>59</sup>          | 2017       | UK      | 39                 | 1                   | f              | NUV                | No                          | C                                    | No                                                                  | LCV            |                                                                           | No                                 | HCQ, CLH, AZA, MMF, MTX (no)                                                                                              | Rituximab, DP (no), OMA (CR)                      |
| Fueyo-Casado <sup>60</sup>   | 2017       | Spain   | 71                 | 1                   | f              | –                  | –                           | C                                    | No                                                                  | NI, LCV        | No <sup>fg,sg</sup>                                                       |                                    | CS+CYC (CR)                                                                                                               | OMA (CR), montelukast+DP (no)                     |
| Diplomatico <sup>39</sup>    | 2017       | Italy   | 17                 | 1                   | f              | NUV                | Yes                         | C                                    | SLE, celiac disease, Graves' disease, <i>M.pneumoniae</i> infection | LCV            |                                                                           | PI*                                |                                                                                                                           | Clarithromycin (CR)                               |
| Hauser <sup>61</sup>         | 2017       | UK      | 24                 | 1                   | m              | HUV                | Yes                         | C                                    | No                                                                  | NI, LCV        | No                                                                        |                                    | CS+CP (CR), CS+MTX (PI)                                                                                                   |                                                   |
| Salim <sup>62</sup>          | 2017       | USA     | 31                 | 1                   | f              | HUVS               | Yes                         | C                                    | No                                                                  | LCV            |                                                                           | PI                                 | CS+CP (CR)                                                                                                                | Antibiotics (no)                                  |
| Sengül Emeksiz <sup>47</sup> | 2016       | Turkey  | 13                 | 1                   | f              | –                  | No                          | A                                    | AIT                                                                 | LCV            | No                                                                        |                                    |                                                                                                                           | Levothyroxine+CS+AHs (CR)                         |
| Zhu <sup>2</sup>             | 2016       | USA     | 50                 | 1                   | f              | NUV (drug-induced) | Yes                         | C                                    | Sarcoidosis                                                         | LCV            | No <sup>fg</sup>                                                          | PI                                 |                                                                                                                           | Drug withdrawal (CR)                              |
| Hübner <sup>63</sup>         | 2016       | Germany | 72                 | 1                   | m              | NUV                | No                          | C                                    | No                                                                  | EI, NI, LCV    | No <sup>sg</sup>                                                          | CR                                 | MTX, CLH (no)                                                                                                             | DP (no)                                           |
| Tracey <sup>64</sup>         | 2016       | USA     | 60                 | 1                   | m              | HUV                | Yes                         | C                                    | No                                                                  | LCV            |                                                                           | PI*                                | CS+DP (PI) <sup>ex</sup>                                                                                                  |                                                   |
| Takao <sup>65</sup>          | 2016       | Japan   | 74                 | 1                   | f              | HUV                | Yes                         | C                                    | IgG4-related disease                                                | LCV            | No                                                                        | CR                                 |                                                                                                                           |                                                   |
| Wong <sup>66</sup>           | 2016       | USA     | 62                 | 1                   | f              | NUV                | Yes                         | A                                    | No                                                                  | NI, EI         |                                                                           |                                    | CS+DP (CR)                                                                                                                |                                                   |
| Chan <sup>67</sup>           | 2016       | Brazil  | 5                  | 1                   | m              | HUV                | No                          | C                                    | No                                                                  | UV, EI         | PI                                                                        | PI*                                |                                                                                                                           |                                                   |

|                            |      |              |       |   |              |                   |         |       |                                      |             |                       |                              |                                                            |                                                  |
|----------------------------|------|--------------|-------|---|--------------|-------------------|---------|-------|--------------------------------------|-------------|-----------------------|------------------------------|------------------------------------------------------------|--------------------------------------------------|
| Fadahuni <sup>68</sup>     | 2015 | USA          | 63    | 1 | f            | HUVS              | Yes     | C     | Psoriatic arthritis                  | LCV         | No <sup>fg,sg</sup>   |                              |                                                            | DP (PI), ustekinumab (no)                        |
| Cherrez Ojeda <sup>5</sup> | 2015 | Ecuador      | 35    | 1 | f            | Drug-induced, NUV | Yes     | A     | –                                    | LI, EI, LCV |                       | CR*                          |                                                            |                                                  |
| Christiansen <sup>69</sup> | 2015 | Sweden       | 71    | 1 | m            | NUV               | No      | C     | Acquired haemophilia                 | LCV         | No                    | No                           | AZA+DP (CR), AZA (CR), CLH+AZA (CR), HCQ (no)              | Tranexamic acid (no),                            |
| Mansard <sup>70</sup>      | 2015 | France       | 18-82 | 4 | –            | –                 | –       | C     | –                                    | –           | No (4/4)              |                              |                                                            | OMA (CR at least in 2/4)                         |
| Koregol <sup>3</sup>       | 2015 | India        | 71    | 1 | m            | Drug-induced, NUV | No      | A     | Diabetes                             | NI, LI, LCV |                       |                              |                                                            | Drug withdrawal+CS (CR)                          |
| Shaigany <sup>40</sup>     | 2015 | USA          | 36    | 1 | m            | NUV               | No      | C     | Neurocysticercosis                   | LCV         |                       |                              |                                                            | Albendazol (CR)                                  |
| Kassim <sup>20</sup>       | 2015 | UK           | 72    | 1 | f            | NUV               | No      | C     | CLL                                  | LCV         | No <sup>fg</sup>      | CR                           |                                                            | H <sub>2</sub> AHs (no), chemotherapy (CR)       |
| Kervarrec <sup>71</sup>    | 2015 | France       | 63    | 1 | f            | HUVS              | Yes     | C     | No                                   | NI, LCV     |                       | CR                           |                                                            |                                                  |
| Mahajan <sup>4</sup>       | 2015 | India        | 53    | 1 | m            | Drug-induced NUV  | No      | A     | No                                   | LI, NI, EI  |                       | CR, CR*                      |                                                            |                                                  |
| Tontini <sup>72</sup>      | 2015 | Italy        | 47    | 1 | f            | HUVS              | Yes     | C     | No                                   | NI, UV      | No                    | No                           | CS+HCQ (no), CS+CYC (PI)                                   |                                                  |
| Ghazanfar <sup>73</sup>    | 2015 | Denmark      | 68    | 1 | m            | –                 | No      | C     | No                                   | NI, LCV     |                       | PI                           |                                                            | DP (no), OMA (CR)                                |
| Koudoukpo <sup>74</sup>    | 2014 | France       | 59    | 1 | m            | NUV               | Yes     | C     | JAK2+ thrombocythemia                | NI, LCV     |                       | CR                           |                                                            | Ruxolitinib (PI-CR)                              |
| Mangal <sup>6</sup>        | 2014 | India        | 11    | 1 | m            | Drug-induced, NUV | No      | A     | No                                   | NI, EI, UV  |                       | CR*                          |                                                            |                                                  |
| Alangari <sup>75</sup>     | 2014 | Saudi Arabia | 10    | 1 | m            | NUV               | Yes     | C     | No                                   | UV          | PI <sup>sg,h</sup>    |                              | HCQ (no)                                                   | DP (CR)                                          |
| Kai <sup>76</sup>          | 2014 | UK           | –     | 1 | –            | NUV               | –       | C     | –                                    | –           | No <sup>h</sup>       |                              |                                                            | OMA (PI)                                         |
| Boules <sup>77</sup>       | 2014 | UK           | 75    | 1 | m            | –                 | Yes     | A     | UC, MG, diabetes                     | NI, EI, LCV |                       | CR                           |                                                            |                                                  |
| Keidel <sup>78</sup>       | 2014 | UK           | 15    | 1 | f            | –                 | Yes     | C     | UAD                                  | LCV         |                       |                              | HCQ, CLH, MMF, AZA, CYC (no)                               | Tocilizumab (CR), anakinra (CR), infliximab (no) |
| Park <sup>79</sup>         | 2014 | Korea        | 30    | 1 | m            | HUVS              | Yes     | C     | No                                   | LCV         |                       | PI                           | CS+CP+MMF (PI)                                             |                                                  |
| Garcia Ponce <sup>80</sup> | 2014 | Spain        | 56    | 1 | f            | NUV               | No      | C     | No                                   | LCV         | No <sup>fg,sg,h</sup> |                              | CLH (no)                                                   | Montelukast, levothyroxine (no), OMA (CR)        |
| Scott <sup>81</sup>        | 2014 | UK           | 32    | 1 | f            | NUV               | No      | C     | Essential thrombocythemia            | LCV, NI     | No <sup>sg</sup>      | PI*                          |                                                            |                                                  |
| Benson <sup>41</sup>       | 2014 | UK           | 32    | 1 | f            | –                 | Yes     | A     | Mycobacterium tuberculosis infection | –           |                       |                              |                                                            | Anti-tuberculosis therapy (CR)                   |
| Pasini <sup>82</sup>       | 2014 | Italy        | 4-9   | 3 | f (2), m (1) | HUVS (3)          | Yes (3) | C (3) | –                                    | LCV         | No (2/2)              | No (1/2), PI (1/2), PI (1/1) | HCQ (no 1/1), CLH (no 1/1), CS+MMF+DP (CR 1/1), CS+CYC+AZA | NSAIDs (no 2/2), anakinra (no 1/1)               |

|                               |      |           |     |              |       |                  |         |        |                                  |                 |                    |                 |                                                                                           |                                                                                                                |
|-------------------------------|------|-----------|-----|--------------|-------|------------------|---------|--------|----------------------------------|-----------------|--------------------|-----------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
|                               |      |           |     |              |       |                  |         |        |                                  |                 |                    |                 | (PI 1/1), CYC (no 1/1), CS+AZA+DP (CR 1/1)                                                |                                                                                                                |
| Sussman <sup>83</sup>         | 2014 | Canada    | –   | 1            | –     | –                | –       | C      | –                                | –               |                    |                 |                                                                                           | OMA (PI)                                                                                                       |
| Bock <sup>7</sup>             | 2014 | Australia | 69  | 1            | f     | Drug-induced     | No      | A      | Breast cancer                    | LI, NI, LCV     |                    |                 |                                                                                           | Drug withdrawal+CS (CR)                                                                                        |
| Krause <sup>84</sup>          | 2013 | Germany   | >40 | 10           | –     | HUV (1), NUV (9) | –       | C (10) | –                                | –               |                    |                 |                                                                                           | Canakinumab (PI 10/10) <sup>ex,1</sup>                                                                         |
| Kolkhir <sup>85</sup>         | 2013 | Russia    | 31  | 1            | f     | HUVS             | Yes     | C      | SLE?                             | UV              | No <sup>n</sup>    | PI              | CS+AZA (CR)                                                                               | Diet (no)                                                                                                      |
| Pinto-Almeida <sup>86</sup>   | 2013 | Portugal  | 49  | 1            | f     | HUV              | No      | C      | HCV                              | NI, LCV         | PI <sup>fg</sup>   |                 |                                                                                           |                                                                                                                |
| Diez <sup>87</sup>            | 2013 | Columbia  | >27 | 3            | f     | NUV (3)          | No (3)  | C (3)  | No                               | LCV (2/3)       | No (2/2)           | No (1/1)        | HCQ (no 1/1), AZA (no 1/1), H <sub>2</sub> AHs <sup>sg</sup> +H <sub>2</sub> AHs (PI 1/1) | OMA (CR 3/3), montelukast (no 2/2), DP (no 1/1), H <sub>2</sub> AHs <sup>sg</sup> +H <sub>2</sub> AHs (PI 1/1) |
| Moiseev <sup>88</sup>         | 2013 | Russia    | –   | 1            | –     | HUV              | Yes     | C      | SLE                              | UV              |                    | PI              |                                                                                           | Rituximab (CR)                                                                                                 |
| Yamazaki <sup>89</sup>        | 2013 | Japan     | 1   | 1            | f     | HUVS             | Yes     | C      | Coxsackievirus type A9 infection | LI, NI, EI, LCV | No                 | CR              |                                                                                           |                                                                                                                |
| Jimenez Ferrera <sup>90</sup> | 2013 | Spain     | 40  | 1            | f     | NUV              | No      | C      | No                               | EI              | No                 | No              | CLH+CS (CR)                                                                               |                                                                                                                |
| Breda <sup>91</sup>           | 2013 | Italy     | 16  | 1            | f     | HUVS             | Yes     | C      | JIA                              | LCV             |                    |                 | HCQ, MTX (no), AZA+IVIG (CR), CS+IVIG (PI)                                                | NSAIDs (no), rituximab+ IVIG (no)                                                                              |
| Ozcakar <sup>92</sup>         | 2013 | Turkey    | 2-6 | 3 (siblings) | f (3) | HUVS (3)         | Yes (3) | C (3)  | No                               | LCV             |                    | PI (2/2)        | CS+CP (PI 2/2), CYC (PI 1/1)                                                              | CS+etanercept (PI 1/1),                                                                                        |
| McGuffin <sup>93</sup>        | 2013 | USA       | 13  | 1            | f     | NUV              | Yes     | C      | No                               | –               |                    | PI <sup>r</sup> |                                                                                           | DP (CR)                                                                                                        |
| Ashida <sup>94</sup>          | 2013 | Japan     | 75  | 1            | f     | HUV              | No      | C      | No                               | LI, NI          |                    | No              | CLH+CS (PI)                                                                               |                                                                                                                |
| Roy <sup>95</sup>             | 2013 | India     | 36  | 1            | f     | HUVS             | Yes     | C      | No                               | EI, LCV         |                    | CR              |                                                                                           |                                                                                                                |
| Makol <sup>96</sup>           | 2012 | USA       | 22  | 1            | f     | HUV              | Yes     | C      | SLE                              | NI              |                    | CR              | MTX, MMF, IVIG, HCQ (no)                                                                  | Anakinra, etanercept (no), tocilizumab (CR)                                                                    |
| Fujimoto <sup>97</sup>        | 2012 | Japan     | 31  | 1            | f     | HUV              | Yes     | C      | –                                | LCV             | No                 |                 | CS+DP (PI), CS+DP+MMF (PI-CR)                                                             | IVIG+CS+MMF+DP (CR)                                                                                            |
| Kamdar <sup>98</sup>          | 2012 | USA       | 32  | 1            | f     | HUV              | Yes     | C      | No                               | EI, UV          | No                 | PI              | CS+DP (PI), CS+HCQ (CR)                                                                   |                                                                                                                |
| Ferguson <sup>99</sup>        | 2012 | USA       | 52  | 1            | f     | HUV              | Yes     | C      | SLE                              | NI, EI          | No                 |                 | CS+HCQ (CR)                                                                               |                                                                                                                |
| Varricchi <sup>100</sup>      | 2012 | Italy     | 44  | 1            | f     | –                | Yes     | C      | Churg-Strauss syndrome           | –               | No                 | No              | CYC, AZA (no)                                                                             | OMA (CR)                                                                                                       |
| Kartal <sup>101</sup>         | 2012 | Turkey    | 35  | 1            | f     | NUV              | No      | C      | No                               | LI, NI, LCV     | No <sup>st,h</sup> | No              | HCQ (no)                                                                                  | H <sub>2</sub> AHs (no), PHS (CR)                                                                              |
| Macedo <sup>102</sup>         | 2012 | Brazil    | 12  | 1            | m     | HUV              | Yes     | C      | SLE, dermatomyositis             | LI, NI, LCV     |                    |                 | CS+DP+MMF (CR)                                                                            |                                                                                                                |
| Buck <sup>103</sup>           | 2012 | USA       | 34  | 1            | m     | HUVS             | Yes     | C      | No                               | NI, LCV         | No                 | PI              | CS+CP (CR), CS+AZA (PI)                                                                   | H <sub>2</sub> AHs, montelukast (no)                                                                           |
| Jones <sup>104</sup>          | 2012 | USA       | 47  | 1            | f     | HUVS             | Yes     | C      | SLE                              | NI              |                    |                 |                                                                                           | DP+CS (CR)                                                                                                     |
| Ferreira <sup>105</sup>       | 2012 | Portugal  | 38  | 1            | f     | NUV              | No      | –      | No                               | LCV, LI         | No                 | CR              |                                                                                           |                                                                                                                |

|                            |      |          |          |    |                |                      |          |        |                                                 |                           |                        |                  |                                                                  |                                                                         |
|----------------------------|------|----------|----------|----|----------------|----------------------|----------|--------|-------------------------------------------------|---------------------------|------------------------|------------------|------------------------------------------------------------------|-------------------------------------------------------------------------|
| Dua <sup>106</sup>         | 2012 | UK       | 38       | 1  | f              | HUV                  | Yes      | C      | <i>M.pneumoniae</i> infection                   | LI, LCV                   | No                     |                  |                                                                  | Co-amoxiclav (no), NSAIDs (CR)                                          |
| Kroshinsky <sup>107</sup>  | 2011 | USA      | 79       | 1  | m              | HUVS                 | Yes      | C      | No                                              | NI, LCV                   |                        | PI               |                                                                  | NSAIDs (no), infliximab (CR)                                            |
| Swaminath <sup>108</sup>   | 2011 | USA      | 26       | 1  | m              | NUV                  | Yes      | C      | UC, MG, CG                                      | NI, LCV                   |                        | PI               | AZA (no)                                                         | Rituximab (CR)                                                          |
| Tronquoy <sup>109</sup>    | 2011 | France   | ≥30      | 10 | m (9), f (1)   | –                    | Yes (10) | C (10) | Polychondritis, hematologic disorders (in some) | LI, NI, LV                |                        | CR (8/8)         | HCQ (no 2/2), CLH (no 1/1)                                       | DP (no 7/7), NSAID <sup>ind</sup> (no 2/2), thalidomide (PI 2/2)        |
| Arslan <sup>110</sup>      | 2011 | Turkey   | 0.5-10   | 15 | f (2), m (13)  | NUV (15)             | No (15)  | C (10) | No                                              | NI (6), LI (9), LCV (all) | CR (6/6)               | CR* (9/9)        |                                                                  |                                                                         |
| Wakamatsu <sup>111</sup>   | 2011 | Japan    | 58       | 1  | f              | HUVS                 | Yes      | C      | RA                                              | LCV                       |                        | CR               |                                                                  |                                                                         |
| Adhya <sup>112</sup>       | 2011 | UK       | –        | 9  | –              | HUV (2)              | –        | C      | SLE (1), Wegener's granulomatosis (1)           | UV                        | PI-CR (2/2)            | PI-CR (1/1)      | CLH (PI-CR 1/2), CYC, MTX+CS+H <sub>1</sub> AHs, HCQ (PI-CR 1/1) | NSAIDs (PI-CR 1/1)                                                      |
| Eliason <sup>113</sup>     | 2010 | USA      | 21-81    | 58 | f (44), m (14) | –                    | –        | C      | –                                               | UV                        |                        |                  |                                                                  | DP (CR 30/58, PR 14/58, no 14/35)                                       |
| Calistru <sup>114</sup>    | 2010 | Portugal | 56       | 1  | f              | HUV                  | Yes      | A      | MCTD                                            | LCV, NI                   | No                     | CR               | CS+HCQ (CR)                                                      |                                                                         |
| Herauld <sup>115</sup>     | 2010 | France   | 43       | 1  | m              | HUVS                 | Yes      | C      | No                                              | LCV                       |                        |                  |                                                                  | DP (PI)                                                                 |
| Abdallah <sup>116</sup>    | 2010 | Tunis    | 46       | 1  | f              | HUVS                 | Yes      | C      | SJS                                             | LCV                       |                        |                  | CS+HCQ (PI)                                                      |                                                                         |
| Demitsu <sup>117</sup>     | 2010 | Japan    | mean: 55 | 8  | m(1), f(7)     | NUV (8)              | –        | C (8)  | Hyperthyroidism and SJS (1)                     | –                         |                        | PI (5/8)         |                                                                  | H <sub>1</sub> AHs+reserpine <sup>1</sup> (CR 6/8, PI 1/8)              |
| Foschi <sup>118</sup>      | 2010 | Greece   | 77       | 1  | f              | NUV                  | No       | C      | HCV, CG                                         | –                         | No                     |                  |                                                                  | PEG-interferon α-2a, ribavirin (CR)                                     |
| Ran Hui Cha <sup>119</sup> | 2010 | Japan    | 65       | 1  | f              | –                    | Yes      | –      | –                                               | LCV                       |                        |                  | CS+CP (PI)                                                       |                                                                         |
| Hughes <sup>8</sup>        | 2010 | France   | 21       | 1  | f              | Vaccine-induced, NUV | No       | A      | No                                              | LCV                       |                        |                  |                                                                  | No revaccination+H <sub>1</sub> AHs (CR)                                |
| Bellini <sup>9</sup>       | 2010 | Italy    | 79       | 1  | m              | Drug-induced         | No       | A      | No                                              | NI, LCV                   |                        |                  |                                                                  | Drug withdrawal+CS (CR)                                                 |
| Perez <sup>120</sup>       | 2010 | UK       | >48      | 4  | m(1), f(3)     | NUV (8)              | –        | C (4)  | –                                               | –                         | No (4/4) <sup>sg</sup> | PI-CR (4/4)      | HCQ (no 3/3), CS+MTX (CR 1/4, PI 2/4), CLH, AZA, CYC, (no 3/3)   | Montelukast (no 4/4), doxepin, DP (no 2/2), IVIG (no 1/1), PTX (no 3/3) |
| Grotz <sup>121</sup>       | 2009 | Germany  | 72       | 1  | f              | HUVS                 | Yes      | C      | No                                              | LCV                       | No                     | No <sup>id</sup> | MMF+CS (CR)                                                      |                                                                         |
| Torres <sup>122</sup>      | 2009 | Spain    | 32       | 1  | m              | NUV                  | Yes      | C      | No                                              | LCV                       |                        | PI               |                                                                  | PTX (CR)                                                                |
| Morgan <sup>123</sup>      | 2009 | USA      | 43       | 1  | f              | –                    | No       | C      | No                                              | LCV                       |                        | PI               | HCQ+CLH (no 1/1), CS+sirolimus (no additional benefit),          | AHs+montelukast (no), CS+etanercept (PI)                                |
| Stigall <sup>124</sup>     | 2009 | USA      | 50       | 1  | m              | NUV                  | No       | C      | No                                              | UV                        |                        | CR               | CS+CLH (PI)                                                      |                                                                         |

|                                     |      |           |       |    |                   |                          |           |        |                            |                 |                             |                            |                                                |                                                                             |
|-------------------------------------|------|-----------|-------|----|-------------------|--------------------------|-----------|--------|----------------------------|-----------------|-----------------------------|----------------------------|------------------------------------------------|-----------------------------------------------------------------------------|
| Her <sup>125</sup>                  | 2009 | Korea     | 50    | 1  | f                 | HUV                      | Yes       | C      | SLE                        | NI, PL          |                             | PI <sup>+</sup>            | CS+MMF (no)                                    | CS+DP (CR)                                                                  |
| Tosoni <sup>126</sup>               | 2009 | Italy     | >11   | 47 | m (14),<br>f (33) | NUV (42), HUV (5)        | Yes (38)  | C (47) | No                         | –               | CR <sup>fg</sup><br>(13/19) | CR <sup>+</sup><br>(13/20) |                                                | H <sub>2</sub> AHs <sup>fg</sup> +CS (CR 13/20)                             |
| Yamazaki-Nakashimada <sup>127</sup> | 2009 | Mexico    | 4     | 1  | f                 | HUV                      | Yes       | C      | SLE                        | LCV             |                             |                            |                                                | IVIG (PI)                                                                   |
| Turner <sup>128</sup>               | 2009 | USA       | 29    | 1  | m                 | NUV                      | Yes       | C      | IgA myeloma                | LCV, NI         |                             |                            | CS+CP (CR)                                     |                                                                             |
| Kennedy <sup>129</sup>              | 2009 | Ireland   | 37    | 1  | f                 | –                        | –         | –      | –                          | –               |                             |                            |                                                | OMA (CR)                                                                    |
| Filosto <sup>130</sup>              | 2009 | Italy     | 62    | 1  | f                 | HUV                      | Yes       | C      | No                         | LCV             |                             | PI                         |                                                |                                                                             |
| Mukhtyar <sup>131</sup>             | 2009 | UK        | 46    | 1  | f                 | NUV                      | No        | C      | No                         | LCV, EI         | No                          |                            | CYC, MTX (no)                                  | H <sub>2</sub> AHs, tranexamic acid, DP, PTX (no), PHS (PI), rituximab (CR) |
| Amano <sup>132</sup>                | 2008 | Japan     | 26    | 1  | f                 | HUVS                     | Yes       | C      | No                         | LCV, NI         | No                          | PI-CR                      | CS+mizoribine (PI-CR), CS+MTX (PI-CR)          |                                                                             |
| Koch <sup>133</sup>                 | 2008 | USA       | <1    | 1  | m                 | NUV                      | Yes       | C      | No                         | NI, EI, LI, LCV | No                          | CR                         |                                                | Montelukast (no)                                                            |
| Saavedra <sup>134</sup>             | 2008 | USA       | 63    | 1  | m                 | NUV                      | No        | C      | No                         | PL, NI, LCV     | PI <sup>sg</sup>            |                            | HCQ (no), DP (CR)                              |                                                                             |
| Cicek <sup>10</sup>                 | 2008 | Turkey    | 48    | 1  | f                 | HUV (drug-induced)       | Yes       | A      | Multiple sclerosis         | NI              |                             | CR                         |                                                |                                                                             |
| Balsam <sup>135</sup>               | 2008 | USA       | 23    | 1  | f                 | HUVS                     | Yes       | C      | No                         | Venulitis       |                             |                            | CS+CP (CR)                                     | Antibiotics (no)                                                            |
| Ghadban <sup>136</sup>              | 2008 | France    | 48    | 1  | f                 | HUVS                     | Yes       | C      | No                         | LCV             | No                          | CR                         | MMF+CP (CR)                                    |                                                                             |
| Jamison <sup>137</sup>              | 2008 | USA       | 41    | 1  | f                 | HUVS                     | Yes       | C      | Lung cancer                | –               |                             | CR                         | CS+CP (CR)                                     |                                                                             |
| Goulao <sup>11</sup>                | 2008 | Portugal  | 61    | 1  | m                 | Drug-induced             | Yes       | A      | Psoriasis                  | LCV, EI, NI     |                             | CR                         |                                                |                                                                             |
| Lipman <sup>138</sup>               | 2007 | UK        | 59    | 1  | m                 | Drug-induced NUV         | Yes       | A      | HIV                        | LCV             |                             | CR                         |                                                | Montelukast (CR)                                                            |
| Melamed <sup>139</sup>              | 2007 | USA       | 40-44 | 2  | f, m              | –                        | –         | C (2)  | AIT                        | UV              | No (2/2)                    | PI (2/2)                   | DP+CLH (CR 1/1), CLH (no 1/1), DP+HCQ (CR 1/1) | DP (PI 1/1), H <sub>2</sub> AHs (no 2/2)                                    |
| Moore <sup>140</sup>                | 2007 | USA       | 83    | 1  | m                 | NUV                      | –         | C      | CLL                        | UV              | No                          | No                         |                                                |                                                                             |
| Brown <sup>141</sup>                | 2007 | USA       | 55    | 1  | f                 | NUV                      | Yes       | C      | Diabetes                   | UV              | PI <sup>fg,sg</sup>         | PI                         | HCQ (no), MTX (CR)                             | Montelukast (no)                                                            |
| Pellizzari <sup>12</sup>            | 2007 | Australia | 40    | 1  | m                 | Formaldehyde-induced NUV | Yes       | A      | No                         | LI, NI, EI      |                             | CR, CR <sup>+</sup>        |                                                |                                                                             |
| Alachkar <sup>142</sup>             | 2007 | UK        | 53    | 1  | f                 | HUVS                     | Yes       | C      | No                         | –               | No                          | PI                         | CS+CP (PI)                                     |                                                                             |
| Shah <sup>143</sup>                 | 2007 | UK        | 59    | 1  | f                 | HUV                      | No        | C      | Non-Hodgkin lymphoma, MG   | LCV, NI         | No                          | CR                         | HCQ (no)                                       | DP (no), IVIG (CR)                                                          |
| Staubach-Renz <sup>144</sup>        | 2007 | Germany   | 37    | 1  | m                 | HUVS                     | Yes       | C      | No                         | LCV, NI         |                             | No <sup>+</sup>            | MTX+CS (PI)                                    | IVIG (CR)                                                                   |
| Yuksel <sup>145</sup>               | 2007 | Turkey    | 8     | 1  | f                 | NUV                      | Yes       | C      | No                         | NI, EI, LCV     |                             | PI                         |                                                |                                                                             |
| Rego <sup>146</sup>                 | 2007 | Brazil    | 71    | 1  | f                 | –                        | No        | C      | HCV, Hodgkin's disease, CG | –               |                             |                            |                                                | PHS (no), rituximab (CR)                                                    |
| Lee <sup>147</sup>                  | 2007 | Malaysia  | >22   | 22 | m(8),             | HUV (2), NUV (20)        | Yes (<11) | C (22) | Churg-Strauss syndrome (1) | NI or LI        |                             | CR (6/10),                 | CS+H <sub>2</sub> AHs+CLH (CR 4/6, PI          |                                                                             |

|                             |      |                      |    |   | f(14) |                    |     |   |                        |             |                     | PI<br>(3/10)* | 2/6)                                        |                                                                                                            |
|-----------------------------|------|----------------------|----|---|-------|--------------------|-----|---|------------------------|-------------|---------------------|---------------|---------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Alizadeh <sup>21</sup>      | 2007 | United Arab emirates | 23 | 1 | m     | HUV                | No  | C | Castleman's disease    | LCV, PL     |                     | CR            | CS+AZA (CR)                                 | Splenectomy (PI)                                                                                           |
| Stinco <sup>148</sup>       | 2007 | Italy                | 41 | 1 | m     | Sun-induced, NUV   | No  | A | No                     | NI, LI, LCV | No <sup>fg,sg</sup> | No            |                                             | H <sub>2</sub> AHs (no)                                                                                    |
| Botsios <sup>149</sup>      | 2007 | Italy                | 54 | 1 | m     | NUV                | Yes | C | No                     | NI, LI      |                     | No            | CYC (no), MTX+CS+naproxen (PI), CYC+CS (no) | Anakinra (CR),                                                                                             |
| Batioglu <sup>150</sup>     | 2006 | Turkey               | 53 | 1 | m     | NUV (drug-induced) | Yes | C | No                     | LI, LCV     |                     |               | CS+HCQ (CR) <sup>ex</sup>                   |                                                                                                            |
| Kato <sup>151</sup>         | 2006 | Japan                | 63 | 1 | f     | NUV                | Yes | C | Systemic sclerosis     | LCV, NI     |                     | CR*           |                                             |                                                                                                            |
| Alexander <sup>152</sup>    | 2006 | USA                  | 46 | 1 | m     | –                  | –   | C | B-cell CLL             | –           |                     |               |                                             | PHS (PI)                                                                                                   |
| Aydogan <sup>153</sup>      | 2006 | Turkey               | 55 | 1 | f     | HUVS               | Yes | C | SLE                    | LCV, NI     |                     | No            | CS+AZA (no)                                 |                                                                                                            |
| Athanasiadis <sup>154</sup> | 2006 | Germany              | 36 | 1 | f     | NUV                | No  | C | AIT, pernicious anemia | LCV         | No <sup>fg,sg</sup> | No            |                                             | Chloroquine+H <sub>2</sub> AH <sup>sg</sup> (CR), H <sub>2</sub> AHsg+montelukast+NSAID+levothyroxine (PI) |
| Lopes <sup>13</sup>         | 2006 | USA                  | 68 | 1 | m     | Drug-induced NUV   | No  | A | NSCLC                  | LI, NI, EI  |                     | CR            |                                             | Antibiotics (no)                                                                                           |
| Eilertsen <sup>22</sup>     | 2006 | Norway               | 36 | 1 | m     | HUV                | Yes | C | Erythroleukemia        | UV          |                     |               | CS+CP, CS+AZA (no)                          | Chemotherapy+allogeneic transplantation of stem cells (CR)                                                 |
| Martin <sup>155</sup>       | 2006 | USA                  | 38 | 1 | m     | HUV                | Yes | C | SLE                    | LCV         | No <sup>fg</sup>    | No            | CP+CS (CR) <sup>ex</sup>                    |                                                                                                            |
| Adler <sup>156</sup>        | 2005 | UK                   | 17 | 1 | f     | HUVS               | Yes | C | No                     | NI          |                     |               | CS+HCQ (no)                                 | Rituximab+CS+MMF (CR)                                                                                      |
| Berti <sup>157</sup>        | 2005 | Italy                | 47 | 1 | f     | HUV                | Yes | C | Subacute CLE           | LCV, NI     |                     |               |                                             | CS+DP (CR)                                                                                                 |
| Husa <sup>158</sup>         | 2005 | Czech Republic       | –  | 1 | m     | –                  | Yes | C | HCV, CG                | –           |                     |               |                                             | Antiviral therapy (CR)                                                                                     |
| Svobodova <sup>33</sup>     | 2005 | Czech Republic       | 43 | 1 | f     | –                  | Yes | C | HCV                    | UV          |                     |               |                                             | Antiviral therapy (CR)                                                                                     |
| Reichenberg <sup>159</sup>  | 2005 | USA                  | 73 | 1 | m     | NUV                | Yes | A | Carcinoma              | NI, LI, LCV |                     | PI-CR         |                                             |                                                                                                            |
| Pisoni <sup>160</sup>       | 2005 | Italy                | 50 | 1 | f     | –                  | Yes | C | SLE                    | LCV         |                     | No            | AZA, MMF (PI), MTX (no)                     | DP, thalidomide (No)                                                                                       |
| Serratrice <sup>161</sup>   | 2005 | France               | 63 | 1 | f     | HUVS               | Yes | C | Polychondritis         | LCV         |                     |               |                                             | CS+DP (CR)                                                                                                 |
| Feiza <sup>14</sup>         | 2005 | Tunis                | 30 | 1 | f     | Drug-induced       | –   | C | –                      | LCV         |                     | PI            |                                             |                                                                                                            |
| Toprak <sup>162</sup>       | 2004 | Turkey               | 53 | 1 | f     | HUVS               | Yes | C | HCV                    | LCV         |                     | CR            |                                             |                                                                                                            |
| Zhang <sup>23</sup>         | 2004 | Japan                | 79 | 1 | m     | NUV                | No  | C | Multiple myeloma       | NI, EI, LCV | No                  |               |                                             | Treatment of myeloma (CR)                                                                                  |
| Zaja <sup>163</sup>         | 2003 | Italy                | 67 | 1 | f     | HUV                | –   | C | HCV, CG                | –           |                     | PI            |                                             | Rituximab (CR)                                                                                             |
| Di Stefano <sup>164</sup>   | 2003 | Italy                | 42 | 1 | m     | NUV                | No  | C | Cystic teratoma        | LCV         |                     |               |                                             | Surgical resection of teratoma (CR)                                                                        |
| Leslie <sup>165</sup>       | 2003 | UK                   | 55 | 1 | f     | –                  | Yes | C | No                     | LCV         |                     |               | HCQ+H <sub>2</sub> AH <sup>sg</sup> (no)    | DP+CS (CR)                                                                                                 |

|                                 |            |          |       |   |       |          |         |       |                                           |             |        |                            |                                                                                                             |                                                         |
|---------------------------------|------------|----------|-------|---|-------|----------|---------|-------|-------------------------------------------|-------------|--------|----------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Jover <sup>42</sup>             | 2003       | Spain    | 51    | 1 | f     | NUV      | Yes     | C     | <i>Mycoplasma pneumoniae</i> infection    | LCV         |        |                            |                                                                                                             | Ceftriaxone, clarithromycin, doxycycline (CR)           |
| Wang <sup>24</sup>              | 2003       | Taiwan   | 37    | 1 | m     | –        | Yes     | C     | Dermatomyositis, carcinoma                | NI, LCV     | No     |                            |                                                                                                             | CS+chemotherapy+radiation therapy (CR)                  |
| Ducarme <sup>26</sup>           | 2003       | France   | 37    | 1 | m     | –        | –       | C     | Renal carcinoma                           | –           |        |                            |                                                                                                             | Curative treatment of carcinoma (CR)                    |
| Saigal <sup>166</sup>           | 2003       | USA      | 40    | 1 | m     | HUVS     | Yes     | C     | SLE                                       | LCV, NI     | No     | MMF (no),                  |                                                                                                             | IVIG+CS (PI), rituximab (CR)                            |
| O'Hare <sup>167</sup>           | 2002       | USA      | 34    | 1 | m     | HUV      | Yes     | C     | MG                                        | LCV         |        | CR                         |                                                                                                             |                                                         |
| DeAmicis <sup>168</sup>         | 2002       | USA      | 12    | 1 | f     | HUV      | Yes     | A     | SLE, AIT                                  | LCV         |        | CR                         |                                                                                                             |                                                         |
| Kelkar <sup>34</sup>            | 2002       | USA      | 29    | 1 | f     | HUV      | No      | C     | HCV                                       | –           | PI     |                            |                                                                                                             | Doxepin (PI-CR), interferon-alfa, and ribavirin (PI-CR) |
| Thorne <sup>169</sup>           | 2002       | USA      | 67    | 1 | m     | HUV      | Yes     | C     | No                                        | LCV         | No     | MTX, CLH (no), CS+MMF (CR) |                                                                                                             | Amoxicillin, doxepin (no)                               |
| Vanness <sup>170</sup>          | 2002       | USA      | 77    | 1 | f     | –        | No      | C     | Chronic natural killer cell lymphocytosis | EI, LCV     |        |                            |                                                                                                             | Doxepin (PI)                                            |
| Wilson <sup>171</sup>           | 2002       | UK       | 56    | 1 | f     | NUV      | Yes     | C     | B-cell non-Hodgkin's lymphoma             | LI          |        | CR                         |                                                                                                             |                                                         |
| Hatice <sup>172</sup>           | 2002       | Turkey   | 55    | 1 | f     | HUV      | No      | A     | HCV, Sweet's syndrome                     | LCV         | No     | CR                         |                                                                                                             |                                                         |
| Grimbert <sup>173</sup>         | 2001       | France   | 36    | 1 | m     | HUVS     | Yes     | C     | No                                        | –           |        |                            |                                                                                                             | PHS (CR) <sup>ex</sup>                                  |
| Saeki <sup>174</sup>            | 2001       | Japan    | 49    | 1 | m     | HUVS     | Yes     | C     | No                                        | LCV, LI     |        | CR                         |                                                                                                             | Antibiotics (no)                                        |
| Miranda <sup>175</sup>          | 2001       | Portugal | 40    | 1 | f     | HUV      | No      | C     | No                                        | LCV         |        | PI                         |                                                                                                             | DP+PTX (CR)                                             |
| Chen <sup>176</sup>             | 2001       | USA      | 27    | 1 | f     | HUVS     | Yes     | C     | No                                        | LCV, NI     | No     | CR                         |                                                                                                             |                                                         |
| el Maghraoui <sup>177</sup>     | 2001       | Morocco  | 39-41 | 2 | f (2) | HUVS (2) | Yes (2) | C (2) | No                                        | LCV         |        | (CR 2/2)                   | CS+CP (PI 1/1)                                                                                              |                                                         |
| Farkas <sup>178</sup>           | 2001       | Hungary  | 40    | 1 | f     | HUV      | Yes     | C     | Acquired C1q-deficiency                   | LCV         |        | PI*                        | HCQ (CR)                                                                                                    |                                                         |
| Soylu <sup>179</sup>            | 2001       | Turkey   | 4     | 1 | f     | NUV      | Yes     | C     | SLE                                       | LCV         | No     |                            | CS+HCQ (CR)                                                                                                 |                                                         |
| Gordon <sup>180</sup>           | 2000       | UK       | 40    | 1 | m     | HUVS     | Yes     | C     | MG, lymphoma, acquired C1q-deficiency     | –           |        | PI                         |                                                                                                             | Chemotherapy (no)                                       |
| Cadnapaphornchai <sup>181</sup> | 2000       | USA      | 4     | 1 | f     | HUVS     | Yes     | C     | JRA                                       | LCV         |        | PI                         |                                                                                                             | DP (CR)                                                 |
| Hong <sup>182</sup>             | 2000       | USA      | 32    | 1 | m     | HUVS     | Yes     | C     | No                                        | NI, LCV     |        | PI                         | HCQ (no), MTX+CS (PI), AZA+CS (PI)                                                                          |                                                         |
| Sessler <sup>183</sup>          | 2000       | Germany  | 40    | 1 | f     | HUVS     | Yes     | C     | No                                        | LCV         |        |                            | CS+CP <sup>ex</sup> (CR)                                                                                    |                                                         |
| Borcea <sup>184</sup>           | 2000       | UK       | 14    | 1 | f     | NUV      | No      | C     | No                                        | NI, EI, LCV | No     |                            | CLH, CYC, AZA, MTX (no)                                                                                     | IVIG (no)                                               |
| Worm <sup>185, 186</sup>        | 2000, 1998 | Germany  | >43   | 2 | f (2) | HUV (2)  | Yes (2) | C (2) | No                                        | EI, LCV     | No (2) |                            | CS+CP (CR 2/2) <sup>ex,i</sup> , IFN $\alpha$ , DP+PTX+CS, CYC, CS+AZA (no 1/1); MMF <sup>ex</sup> (CR 2/2) | CS+IVIG, DP+PTX (no 2/2),                               |

|                                  |      |             |       |   |       |                      |           |       |                                        |             |                     |          |                                      |                                                                         |
|----------------------------------|------|-------------|-------|---|-------|----------------------|-----------|-------|----------------------------------------|-------------|---------------------|----------|--------------------------------------|-------------------------------------------------------------------------|
| Purello-D'Ambrosio <sup>43</sup> | 1999 | Italy       | 32    | 1 | f     | HUV                  | Yes       | C     | <i>Trichomonas vaginalis</i> infection | LCV         | PI                  |          |                                      | Diet (no), metronidazol (CR)                                            |
| Nishijima <sup>187</sup>         | 1999 | Japan       | –     | 2 | –     | HUV (2)              | –         | C (2) | SLE                                    | LCV         |                     | PI (2/2) | CS+DP (CR 1/1),<br>CS+DP+CP (CR 1/1) |                                                                         |
| Hofbauer <sup>48</sup>           | 1999 | Switzerland | 24    | 1 | m     | Cocaine-induced, NUV | Yes       | A     | No                                     | LI, NI, LCV |                     | CR*      |                                      | Withdrawal of cocaine+CS+H <sub>2</sub> AHs (CR)                        |
| Nawate <sup>188</sup>            | 1998 | Japan       | 61    | 1 | m     | –                    | Yes       | C     | No                                     | NI, UV      |                     |          |                                      | DP (PI-CR)                                                              |
| Hamid <sup>189</sup>             | 1998 | USA         | 37-52 | 2 | f (2) | HUV (1)              | Yes (1/1) | C (2) | HCV                                    | EI, LI, LCV |                     |          |                                      | Interferon $\alpha$ -2 $\beta$ (CR 2/2)                                 |
| Bolla <sup>190</sup>             | 1998 | France      | 56    | 1 | m     | NUV                  | Yes       | C     | No                                     | LCV         |                     | PI       |                                      | CS+DP (PI)                                                              |
| Renard <sup>191</sup>            | 1998 | Belgium     | 5     | 1 | m     | HUV                  | Yes       | C     | No                                     | –           | No                  | CR       | CS+AZA (CR)                          | NSAIDs (no)                                                             |
| Eads <sup>192</sup>              | 1998 | USA         | 30    | 1 | m     | NUV                  | Yes       | A     | No                                     | NI          | No <sup>fg</sup>    | CR       |                                      | Doxepin (no)                                                            |
| Werder <sup>193</sup>            | 1997 | Switzerland | 45    | 1 | f     | HUV                  | Yes       | C     | No                                     | EI, LCV     | No                  | No       | HCQ (CR)                             |                                                                         |
| Eiser <sup>194</sup>             | 1997 | USA         | 35    | 1 | f     | HUV                  | Yes       | C     | No                                     | –           |                     | PI*      | CS+CP (no), CLH (no),                | NSAIDs, PTX (no), DP (CR)                                               |
| Ishikawa <sup>195</sup>          | 1997 | Japan       | 33    | 1 | m     | HUV                  | Yes       | C     | –                                      | LCV, NI     |                     | PI       |                                      |                                                                         |
| Loche <sup>15</sup>              | 1997 | France      | –     | 1 | –     | Drug-induced         | –         | A     | –                                      | –           |                     |          |                                      | Drug withdrawal (CR)                                                    |
| Matteson <sup>36</sup>           | 1996 | USA         | 68    | 1 | f     | –                    | –         | C     | Hepatitis A                            | –           | No                  | No       | MTX, HCQ, AZA (no)                   | H <sub>2</sub> AHs, NSAIDs, IVIG, PHS, DP (no), Interferon alfa 2a (CR) |
| Licht-Mbalyohere <sup>196</sup>  | 1996 | Germany     | –     | 1 | f     | –                    | –         | C     | SLE                                    | UV          |                     |          |                                      | Extracorporeal photochemotherapy (PI)                                   |
| Hey <sup>197</sup>               | 1996 | Germany     | 39    | 1 | f     | NUV                  | –         | C     | No                                     | –           | No                  | No       |                                      | DP (CR)                                                                 |
| Farell <sup>27</sup>             | 1996 | UK          | 77    | 1 | m     | NUV                  | No        | C     | Polycythemia rubra vera                | LI, EI      | PI-CR <sup>sg</sup> |          |                                      | Allopurinol (CR), phlebotomy (CR)                                       |
| Kuniyuki <sup>198</sup>          | 1996 | Japan       | 56    | 1 | m     | NUV                  | No        | C     | HCV, CG                                | LCV, NI, LI |                     | No*      | AZA (PI-CR)                          | CS+NSAID <sup>ind</sup> +CLH (CR)                                       |
| Mukkamala <sup>199</sup>         | 1996 | USA         | 36    | 1 | f     | HUV                  | Yes       | C     | No                                     | NI, PL, LCV | No                  | PI       | CLH+CS (CR)                          | H <sub>2</sub> AHs (no)                                                 |
| Demierre <sup>200</sup>          | 1996 | USA         | 54    | 1 | m     | –                    | Yes       | C     | MG                                     | LCV         | No                  | PI       | CLH (no), CS+AZA (CR)                | DP (no)                                                                 |
| Papadavid <sup>16</sup>          | 1996 | UK          | 39    | 1 | f     | Drug-induced, HUV    | Yes       | A     | No                                     | LCV, EI     | No <sup>fg</sup>    | CR       |                                      |                                                                         |
| Blanco <sup>201</sup>            | 1996 | Spain       | 40    | 1 | f     | NUV                  | Yes       | C     | Megakaryocytic leukemia                | NI, LCV     |                     |          |                                      | NSAIDs <sup>ind</sup> (PI)                                              |
| Menikoff <sup>202</sup>          | 1995 | USA         | 41    | 1 | m     | HUV                  | Yes       | C     | HCV                                    | LCV         | PI-CR               |          |                                      |                                                                         |
| Lin <sup>203</sup>               | 1995 | USA         | 42    | 1 | m     | HUV                  | Yes       | C     | HCV                                    | LCV         |                     | PI       | CS+AZA+DP (PI)                       |                                                                         |
| Karlsberg <sup>37</sup>          | 1995 | USA         | 31    | 1 | f     | –                    | –         | C     | HCV                                    | LCV         |                     |          |                                      | Interferon alfa (CR)                                                    |
| Cohen <sup>204</sup>             | 1995 | USA         | 54    | 1 | f     | HUV                  | Yes       | C     | SLE                                    | LCV, NI     |                     | CR       | HCQ (no), CLH (PI)                   | DP+CS (CR)                                                              |
| Strickland <sup>205</sup>        | 1995 | USA         | 15    | 2 | f (2) | HUV (2)              | Yes (2)   | C (2) | Hodgkin's disease                      | NI, LCV     |                     | CR (2/2) |                                      | DP (CR)                                                                 |
| Roger <sup>206</sup>             | 1995 | France      | 49    | 1 | f     | Drug-induced         | No        | A     | No                                     | LCV         |                     |          |                                      | Drug withdrawal (CR)                                                    |
| Sais <sup>207</sup>              | 1995 | Spain       | >18   | 2 | –     | –                    | –         | C     | –                                      | –           |                     |          | CLH (PI-CR 1/2)                      |                                                                         |

|                               |            |             |         |                 |              |                       |           |        |                                                                                             |                       |                  |                                  |                                                                                                                        |                                                                                             |
|-------------------------------|------------|-------------|---------|-----------------|--------------|-----------------------|-----------|--------|---------------------------------------------------------------------------------------------|-----------------------|------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Kao <sup>208</sup>            | 1995       | USA         | 49      | 1               | f            | NUV                   | Yes       | C      | Polymyositis                                                                                | LV                    | No               | PI                               |                                                                                                                        |                                                                                             |
| Wisnieski <sup>209, 210</sup> | 1995, 1994 | USA         | 32-76   | 18 (incl twins) | m(3), f(15)  | HUVS (18)             | Yes (18)  | C (18) | SLE (in some)                                                                               | NI and/or LI, LCV     | No (18/18)       | PI-CR <sup>ex</sup> (in most/17) | HCQ (PI 2/2), CS+HCQ <sup>ex</sup> (CR 2/3, PI 1/3), DP+AZA, AZA, CS+DP, IVIG (CR <sup>ex</sup> , 1/2), CLH (no 18/18) | H <sub>2</sub> AHs (no 18/18), NSAIDs (no 18/18), danazol, doxepin (no 18/18), DP (PI 5/5), |
| Nürnberg <sup>211</sup>       | 1994       | Germany     | 40      | 1               | f            | HUVS                  | Yes       | C      | No                                                                                          | LCV                   |                  |                                  |                                                                                                                        | DP, PTX (PI), PTX+DP (CR <sup>ex</sup> )                                                    |
| Sprossmann <sup>28</sup>      | 1994       | Germany     | 30      | 1               | m            | –                     | –         | C      | Malignant testicular teratoma                                                               | –                     |                  |                                  |                                                                                                                        | Surgical and chemotherapy therapy of teratoma (PI-CR)                                       |
| Stack <sup>212</sup>          | 1994       | USA         | –       | 1               | –            | –                     | –         | C      | –                                                                                           | –                     |                  | PI-CR                            | MTX (CR)                                                                                                               |                                                                                             |
| Kobayashi <sup>213</sup>      | 1994       | Japan       | 28-55   | 2               | m (1), f (1) | HUV (2)               | Yes (2)   | C (2)  | Graves' disease                                                                             | LCV                   | No (2/2)         | No (2/2), No (1/1)               |                                                                                                                        |                                                                                             |
| Martini <sup>214</sup>        | 1994       | USA         | 15      | 1               | m            | HUVS                  | Yes       | C      | No                                                                                          | LCV                   |                  | CR <sup>ex</sup>                 | CS+CP (PI) <sup>ex</sup> , CS+DP+AZA (no)                                                                              |                                                                                             |
| Stevens <sup>215</sup>        | 1994       | UK          | 9       | 1               | m            | HUVS                  | Yes       | C      | UC, SLE                                                                                     | NI, EI, LCV           |                  |                                  | CS+AZA (CR)                                                                                                            |                                                                                             |
| Paira <sup>216</sup>          | 1994       | Argentina   | 32      | 1               | f            | NUV                   | Yes       | C      | No                                                                                          | LCV                   | No               | PI                               | CLH (no)                                                                                                               | NSAIDs (no) <sup>ind</sup> , DP (no)                                                        |
| Rakita <sup>45</sup>          | 1993       | USA         | 38      | 1               | m            | –                     | No        | C      | Filariasis                                                                                  | NI, EI, LCV           | PI               |                                  |                                                                                                                        | Diethylcarbamazine (CR)                                                                     |
| Wüthrich <sup>49</sup>        | 1993       | Switzerland | 47      | 1               | m            | Disulfite-induced NUV | No        | C      | No                                                                                          | NI, EI, LCV           |                  | PI*                              |                                                                                                                        | Avoidance of sulfited foods and drugs (CR)                                                  |
| Lacour <sup>217</sup>         | 1993       | France      | 75      | 1               | f            | NUV                   | No        | A      | Renal carcinoma                                                                             | NI, LCV               |                  |                                  |                                                                                                                        | Nephrectomy (CR)                                                                            |
| Misery <sup>44</sup>          | 1993       | France      | 21      | 1               | m            | HUV                   | Yes       | C      | BCG infection?                                                                              | EI, LV                |                  |                                  |                                                                                                                        | Rifampicin+isoniazid (CR)                                                                   |
| Pakula <sup>218</sup>         | 1993       | USA         | 57      | 1               | m            | HUV                   | No        | C      | HCV, CG                                                                                     | LCV                   | No <sup>19</sup> | No                               |                                                                                                                        |                                                                                             |
| Kwon <sup>219</sup>           | 1993       | Korea       | 23      | 1               | f            | NUV                   | No        | A      | No                                                                                          | LI, NI, EI, LCV       |                  | CR                               |                                                                                                                        |                                                                                             |
| Garcia-Fuentes <sup>220</sup> | 1992       | Spain       | 5       | 1               | f            | NUV                   | Yes       | C      | –                                                                                           | NI                    |                  | PI                               |                                                                                                                        | NSAIDs (CR) <sup>ind,ex</sup>                                                               |
| Mehregan <sup>221</sup>       | 1992       | USA         | mean 48 | 72              | m(29), f(43) | HUV (23), NUV (49)    | Yes (>35) | C (72) | SLE (8), hematologic malignancy (6), IBD (1), solid tumors (2), Guillain-Barré syndrome (1) | PL, EI and/or LI, LCV | CR-PI (20/37)    | CR-PI (23/27)                    | HCQ (CR-PI 14/26), AZA (CR-PI 2/4), CP (CR-PI 1/1), CLH (no 2/2)                                                       | H <sub>2</sub> AHs (no 4/4), NSAIDs (CR-PI 15/25)                                           |
| Fonseca <sup>222</sup>        | 1992       | Brazil      | 37      | 1               | f            | HUV                   | Yes       | C      | No                                                                                          | LCV                   | No               | PI                               | CLH (no)                                                                                                               | H <sub>2</sub> AHs (no), DP (CR)                                                            |
| Epstein <sup>223</sup>        | 1992       | USA         | 35      | 1               | f            | NUV                   | No        | C      | No                                                                                          | NI                    | No               | CR                               |                                                                                                                        | Elimination diet (CR)                                                                       |
| Carsuzaa <sup>30</sup>        | 1992       | France      | 73      | 1               | m            | –                     | –         | C      | Renal adenocarcinoma                                                                        | UV                    |                  |                                  |                                                                                                                        | Treatment of cancer (CR)                                                                    |
| Asherson <sup>224</sup>       | 1992       | UK          | 40      | 1               | f            | HUV                   | Yes       | C      | IgA deficiency, C1-inhibitor                                                                | PI, LCV               | No               | PI                               | CS+CP (PI), HCQ, CLH,                                                                                                  | H <sub>2</sub> AHs, DP, danazol (no)                                                        |

|                                |      |             |       |    |               |                              |                 |        | deficiency, MG     |                  |                         |                           | AZA, (no)                                         |                                                                                      |
|--------------------------------|------|-------------|-------|----|---------------|------------------------------|-----------------|--------|--------------------|------------------|-------------------------|---------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------|
| Asherson <sup>225</sup>        | 1991 | UK          | 47    | 1  | f             | NUV                          | Yes             | C      | No                 | NI, LCV          | No                      | PI                        | HCQ, CP (no),<br>CLH (CR)                         | NSAIDs (no), DP (No)                                                                 |
| Merle <sup>226</sup>           | 1991 | France      | 35    | 1  | m             | HUVS                         | Yes             | C      | CG                 | LCV              |                         |                           |                                                   | CS+DP (PI)                                                                           |
| Lee <sup>227</sup>             | 1991 | South Korea | 19    | 1  | f             | NUV                          | Yes             | C      | No                 | LCV              |                         | PI                        |                                                   | DP (CR)                                                                              |
| Asherson <sup>228</sup>        | 1991 | UK          | >16   | 27 | f (24), m (3) | NUV (5), HUV (in most of 22) | Yes (>13)       | C (27) | SLE (18), MCTD (1) | LCV (in most)    |                         | PI-CR (5/5) <sup>hd</sup> | CP (PI-CR 5/5), CLH (CR 1/1)                      | PHS, cromoglycate, DP, AZA, NSAIDs (no in some patients), danazol (no 1/1)           |
| Mosovich <sup>18</sup>         | 1991 | Israel      | 29    | 1  | f             | Drug-induced                 | –               | A      | –                  | –                |                         |                           |                                                   | Withdrawal of drug                                                                   |
| Handfield-Jones <sup>229</sup> | 1991 | UK          | 45    | 1  | f             | HUV                          | Yes             | C      | No                 | –                | No                      | CR                        | CLH+CS (PI),                                      | DP (PI), gold therapy (CR)                                                           |
| Holtman <sup>230</sup>         | 1990 | USA         | –     | 1  | –             | –                            | Yes             | C      | SjS, SCLE          | UV               |                         |                           |                                                   | DP (CR)                                                                              |
| Olson <sup>46</sup>            | 1990 | USA         | 4     | 1  | f             | NUV                          | Yes             | C      | Lyme disease       | LI, EI           |                         |                           |                                                   | Penicillin (CR)                                                                      |
| Jones <sup>231</sup>           | 1990 | USA         | 40    | 1  | f             | HUV                          | Yes             | C      | No                 | PL, EI           |                         | CR                        |                                                   |                                                                                      |
| Shibasaki <sup>232</sup>       | 1989 | Japan       | 26    | 1  | f             | HUV                          | Yes             | C      | MCTD               | LCV              |                         | CR                        |                                                   |                                                                                      |
| Catrani <sup>233</sup>         | 1989 | Italy       | –     | 1  | –             | –                            | –               | –      | –                  | UV               |                         |                           |                                                   | DP (PI-CR)                                                                           |
| Borradori <sup>234</sup>       | 1989 | France      | 46    | 1  | f             | HUV                          | No              | C      | G3NeF-mutation     | LCV, NI          | No                      | PI                        | CLH (no)                                          | DP (no)                                                                              |
| Bisaccia <sup>235</sup>        | 1988 | USA         | 30    | 1  | f             | HUV                          | Yes             | C      | SLE, AIT           | NI, EI, LCV      | No <sup>fg</sup>        | CR                        | CLH (no)                                          | H <sub>2</sub> AHs (no), H <sub>1</sub> AH <sup>fg</sup> +NSAID (CR)                 |
| Berg <sup>236</sup>            | 1988 | USA         | >24   | 3  | m (2), f (1)  | NUV (3)                      | Yes (2), no (1) | C (3)  | No                 | NI, LCV          | No-PI <sup>fg</sup>     |                           |                                                   | H <sub>1</sub> AH <sup>fg</sup> +doxepin (PI 1/1)                                    |
| Yasue <sup>237</sup>           | 1987 | Japan       | 64    | 1  | f             | HUV                          | Yes             | C      | CG                 | NI               | No                      |                           |                                                   | DP (CR), DP+CS (CR)                                                                  |
| Wozel <sup>238</sup>           | 1987 | Germany     | –     | 1  | f             | HUV                          | –               | C      | –                  | –                | No                      |                           | CLH (no)                                          | H <sub>2</sub> AHs, NSAIDs <sup>ind</sup> (no), DP (PI) <sup>i</sup>                 |
| Granier <sup>50</sup>          | 1987 | France      | –     | 1  | –             | NUV                          | Yes             | C      | AIT                | LCV              |                         |                           |                                                   | Levothyroxine (CR)                                                                   |
| Callen <sup>239</sup>          | 1987 | USA         | 19-86 | 16 | –             | –                            | –               | C (16) | In some            | LCV              | PI <sup>fg</sup> (4/17) | PI-CR (16/16)             | CLH+CS (PI 1/2), AZA+CS (no 1/1), HCQ+CS (no 2/2) | NSAIDs (PI 1/4), DP+CS (no 2/2)                                                      |
| Ramirez <sup>240</sup>         | 1987 | USA         | 59    | 1  | m             | HUV                          | Yes             | C      | No                 | PL               |                         |                           | CS+CP (CR) <sup>i</sup> , CS+AZA (no)             |                                                                                      |
| Aboobaker <sup>241</sup>       | 1986 | UK          | 24-68 | 15 | f (12), m (3) | HUV (3), NUV (12)            | Yes (9)         | C (15) | SLE (1), SjS       | LCV (12), LV (3) | PI-CR (4/13)            | PI-CR (3/5)               |                                                   | PHS (no 1/1), NSAIDs (PI-CR 4/8), DP (PI-CR 4/11)                                    |
| Fortson <sup>242</sup>         | 1986 | USA         | 45    | 1  | f             | HUVS                         | Yes             | C      | No                 | LCV              | PI <sup>fg</sup>        | CR                        | CLH (no)                                          | NSAIDs (no) <sup>ind</sup> , tetracycline, erythromycin, sulfapyridine (no), DP (CR) |
| Werni <sup>243</sup>           | 1986 | Austria     | 72    | 1  | f             | HUV                          | Yes             | C      | No                 | NI               |                         | PI                        | CLH (CR)                                          | NSAIDs (no), DP (no)                                                                 |
| Wiles <sup>244</sup>           | 1985 | USA         | >29   | 2  | f (2)         | NUV (1), HUV (1)             | Yes (2)         | C (2)  | CG                 | NI               | No (1/1)                | No (2/2)                  | CLH (CR 2/2)                                      | H <sub>2</sub> AHs (no 1/1), AHs <sup>fg</sup> +NSAID <sup>ind</sup> (no 1/1)        |
| Muramatsu <sup>245</sup>       | 1985 | Japan       | 51    | 1  | f             | NUV                          | No              | C      | No                 | NI               | No                      |                           | CLH (CR)                                          | DP (PI)                                                                              |
| Falk <sup>246</sup>            | 1984 | USA         | 45    | 1  | f             | HUV                          | Yes             | C      | No                 | LCV              | No <sup>fg</sup>        | CR                        |                                                   |                                                                                      |
| Lopez <sup>247</sup>           | 1984 | USA         | 31    | 1  | m             | HUVS                         | Yes             | C      | No                 | LCV, NI, EI      | No                      | No                        | HCQ (CR), AZA (no)                                | H <sub>2</sub> AHs, NSAIDs (no)                                                      |

|                              |      |             |       |    |              |                    |                     |        |                       |                             |                        |                                 |                                                |                                                                    |
|------------------------------|------|-------------|-------|----|--------------|--------------------|---------------------|--------|-----------------------|-----------------------------|------------------------|---------------------------------|------------------------------------------------|--------------------------------------------------------------------|
| Newton <sup>248</sup>        | 1984 | UK          | >60   | 2  | m (2)        | NUV (1), HUV (1)   | No (NUV), Yes (HUV) | C (2)  | IBD (2), diabetes (1) | EI (1), LCV                 |                        | PI (1/1) <sup>ex</sup>          | CLH (CR 1/1)                                   | DP (PI 1/1), sulfasalazine (CR 1/1)                                |
| Duschet <sup>249</sup>       | 1984 | Germany     | 72    | 1  | f            |                    | Yes                 | C      | No                    | LCV                         |                        | PI                              |                                                |                                                                    |
| Wanderer <sup>250</sup>      | 1983 | USA         | 37    | 1  | f            | HUV                | Yes                 | C      | Melanoma              | LCV, PL                     |                        | CR                              |                                                | NSAIDs (no) <sup>ind</sup>                                         |
| Mitchell <sup>251</sup>      | 1983 | USA         | 63    | 1  | m            | Drug-induced       | No                  | A      | No                    | LI, LCV                     | No <sup>fg</sup>       | CR                              |                                                | Withdrawal of the drug+CS (CR)                                     |
| Jones <sup>252</sup>         | 1983 | UK          | >32   | 3  | f (3)        | HUV (2), NUV (1)   | Yes (3)             | C (3)  | No                    | NI, LCV                     | No(3/3) <sup>fg</sup>  | PI (2/2)                        |                                                | NSAIDs (no 2/2) <sup>ind</sup> , DP (CR 1/3, PR 2/3), PHS (CR 2/2) |
| Schwartz <sup>253</sup>      | 1982 | USA         | >17   | 16 | m(3), f(13)  | HUV (16)           | Yes (16)            | C (16) | No                    | –                           | No (4/4)               | PI (4/4)                        | HCQ (no 4/4)                                   | NSAIDs (no 4/4) <sup>ind</sup> , DP (no 4/4)                       |
| Sanchez <sup>254</sup>       | 1982 | USA         | >17   | 40 | m(13), f(27) | HUV (16), NUV (24) | Yes (>20)           | C (40) | No                    | LCV                         |                        | CR-PI (13/17)                   | CP (PI 1/2)                                    | NSAIDs <sup>2</sup>                                                |
| Callen <sup>255</sup>        | 1982 | USA         | >2    | 9  | m(5), f(4)   | HUV (2), NUV (7)   | Yes (<5)            | C (9)  | SLE (1)               | PL, LCV                     | CR (1/9), PR (7/9)     | CR-PI (6/7)                     | HCQ (no 3/3), AZA+CS (PI 1/1)                  | NSAIDs (no 4/4) <sup>ind</sup> , DP+CS (PI 1/1)                    |
| Popp <sup>38</sup>           | 1981 | USA         | 22-32 | 3  | f (1), m (2) | HUV (2)            | Yes (3)             | A (3)  | Acute hepatitis B (3) | LI, LV (3)                  |                        |                                 |                                                | Clearing after acute hepatitis B (CR 3/3)                          |
| Van der Horst <sup>256</sup> | 1981 | Netherlands | 56    | 1  | m            | HUV                | Yes                 | C      | SLE                   | EI, LCV                     |                        |                                 | CS+HCQ (CR)                                    |                                                                    |
| Ruzicka <sup>257</sup>       | 1981 | Germany     | 33    | 1  | f            | HUV                | Yes                 | C      | SLE, psoriasis        | –                           |                        | PI                              | CS+AZA (no), CS+AZA+DP (CR)                    |                                                                    |
| Schultz <sup>258</sup>       | 1981 | USA         | >35   | 2  | m (1), f (1) | HUVS (2)           | Yes (2)             | C (2)  | SLE?                  | LI, NI                      | No (1/1)               | CR (1/1), PI (1/1) <sup>*</sup> |                                                |                                                                    |
| Highet <sup>259</sup>        | 1980 | UK          | 44    | 1  | m            | HUV                | No                  | C      | IgA myeloma           | UV                          | No                     | CR                              |                                                | CS+melphalan (CR)                                                  |
| Millns <sup>260</sup>        | 1980 | USA         | >16   | 10 | m(5), f(5)   | NUV (9), HUV (1)   | Yes (10)            | C (10) | No                    | LI, NI, LCV                 |                        |                                 |                                                | NSAIDs (CR <sup>ind</sup> , ex 6/10, PI <sup>ind</sup> , ex 3/10)  |
| Ludivico <sup>261</sup>      | 1979 | USA         | 24    | 1  | f            | HUVS               | Yes                 | C      | Pseudotumor cerebri   | LI, NI, UV                  | No <sup>fg</sup>       | PI <sup>*</sup>                 |                                                |                                                                    |
| O'Loughlin <sup>262</sup>    | 1978 | USA         | >22   | 9  | m (5), f (4) | HUV (>4)           | Yes (9)             | C (9)  | SLE (9)               | EI (2), PL (1), LI (1), LCV |                        | PI (3/3) <sup>*</sup>           |                                                |                                                                    |
| Gammon <sup>263</sup>        | 1979 | USA         | 33    | 1  | f            | HUV                | Yes                 | C      | No                    | LCV                         | No                     | CR, CR <sup>*</sup>             |                                                |                                                                    |
| Mathison <sup>264</sup>      | 1977 | USA         | >35   | 2  | f (2)        | HUV (2)            | Yes (1), no (1)     | C (2)  | No                    | LCV                         | PI <sup>fg</sup> (1/2) | No (2/2)                        | CLH (no 1/1)                                   |                                                                    |
| Marder <sup>265</sup>        | 1976 | USA         | 46    | 1  | f            | HUV                | Yes                 | C      | C1q deficiency        | LCV                         | No                     | PI-CR                           |                                                | Diuretics, NSAIDs (no)                                             |
| Geha <sup>266</sup>          | 1976 | Lebanon     | 6     | 1  | f            | HUV                | No                  | C      | No                    | EI                          |                        | CR                              |                                                | Antihelmintics (no)                                                |
| Sissons <sup>267</sup>       | 1974 | UK          | >47   | 2  | f (2)        | HUV (2)            | Yes (1), no (1)     | C (2)  | No                    | EI, NI                      | No (1/1)               | PI (2)                          | CS+CP (PI 1/1) <sup>ex</sup> , CS+AZA (no 1/1) | H <sub>1</sub> AHs <sup>fg</sup> +NSAIDs <sup>ind</sup> (PI 1/1)   |
| McCombs <sup>268</sup>       | 1956 | USA         | 40-53 | 3  | f(1), m(2)   | –                  | Yes (1), no (2)     | C (3)  | No                    | EI (2), UV                  | PI (1/2)               | CR (1/1)                        |                                                | H <sub>1</sub> AHs+NSAIDs (PI 1/1)                                 |

<sup>st</sup>standard dose; <sup>h</sup>high dose; <sup>ld</sup>low dose; <sup>fg</sup>first generation antihistamines; <sup>sg</sup>second generation antihistamines; <sup>ind</sup>indomethacin; <sup>i</sup>immunological remission; <sup>ex</sup>remission of extracutaneous symptoms; \*+H<sub>1</sub>AHs; <sup>1</sup>statistically significant; <sup>2</sup>some of the patients treated with NSAIDs were described in another study (Millns et al., 1980); UV: urticarial vasculitis; A: acute UV; C: chronic UV; HUV: hypocomplementemic urticarial vasculitis; HUVS: hypocomplementemic urticarial vasculitis syndrome; NUV: normocomplementemic urticarial vasculitis; f: female; m: male; CR: complete cutaneous remission; PI: partial cutaneous improvement; PHS: plasmapheresis; CS: corticosteroids; HCQ: hydroxychloroquine; CP: cyclophosphamide; DP: dapsone; PTX: pentoxifylline; AZA: azathioprine; CYC: cyclosporine; IVIG: intravenous immunoglobulins; CLH: colchicine; AHs: antihistamines; MTX: methotrexate; NSAIDs: nonsteroidal antiinflammatory drugs; MMF: mycophenolate mofetil; OMA: omalizumab; UC: ulcerative colitis; MG: monoclonal gammopathy; NI: a predominantly neutrophil infiltrate; EI: a predominantly eosinophil infiltrate; LI: a predominantly lymphocytic infiltrate; PL: predominantly polymorphonuclear leukocytes; LCV: leukocytoclastic vasculitis; LV: lymphocytic vasculitis; JIA: juvenile idiopathic arthritis; CG: cryoglobulinemia; HCV: hepatitis C infection; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; MCTD: mixed connective tissue disease; NSCLC: non-small cell lung cancer; SCLE: subacute cutaneous lupus erythematosus; JRA: juvenile rheumatoid arthritis; IBD: inflammatory bowel disease; CLL: chronic lymphocytic leukemia; UAD: undifferentiated autoimmune disorder; SjS Sjogren's syndrome; AIT: autoimmune thyroiditis

Suppl. Table 6. The drugs successfully used for the treatment of chronic (&gt;6 weeks) urticarial vasculitis

| First author, year                       | UV patients benefited, n | Age, y | UV subgroup | Extracutaneous symptoms | Underlying disease            | Treatment         |                    | Efficacy of treatment |                                                | Improvement of urticarial rash |             | Relapse of urticarial rash after tapering of the dose or drug withdrawal |
|------------------------------------------|--------------------------|--------|-------------|-------------------------|-------------------------------|-------------------|--------------------|-----------------------|------------------------------------------------|--------------------------------|-------------|--------------------------------------------------------------------------|
|                                          |                          |        |             |                         |                               | An initial dose   | Duration           | Skin symptoms         | Extracutaneous symptoms and laboratory markers | Seen within                    | Duration, y |                                                                          |
| PREDNISOLONE                             |                          |        |             |                         |                               |                   |                    |                       |                                                |                                |             |                                                                          |
| Jachiet 2015, 2017 <sup>56, 57</sup>     | 22/32                    | >14    | HUV         | Yes (in most)           | Yes, in some                  | 40 mg/d           | Several months     | PI-CR                 | ↓ (in most patients)                           | –                              | –           | –                                                                        |
| Takao 2016 <sup>65</sup>                 | 1/1                      | 74     | HUV         | Yes                     | IgG-related disease           | 10-20 mg/d        | –                  | CR                    | ↓lymph node swelling, ↓IgG4                    | –                              | –           | Yes                                                                      |
| Kroshinsky 2011 <sup>107</sup>           | 1/1                      | 79     | HUVS        | Yes                     | No                            | 40 mg/d           | Several months     | PI                    | ↓JS                                            | –                              | –           | Yes                                                                      |
| Perez 2010 <sup>120</sup>                | 4/4                      | 49-63  | NUV         | –                       | –                             | 10-60 mg/d        | –                  | PI-CR                 | –                                              | –                              | –           | –                                                                        |
| Morgan 2009 <sup>123</sup>               | 1/1                      | 43     | –           | No                      | No                            | 40 mg/d           | –                  | PI                    | –                                              | –                              | –           | –                                                                        |
| Amano 2008 <sup>132</sup>                | 1/1                      | 26     | HUVS        | Yes                     | No                            | 30 mg/d           | Several years      | PI-CR                 | ↓JS                                            | –                              | –           | Yes                                                                      |
| Ghadban 2008 et al. <sup>136</sup>       | 1/1                      | 48     | HUVS        | Yes                     | No                            | 1 mg/kg/d         | 18 months          | CR                    | ↓OS, JS                                        | –                              | –           | Yes                                                                      |
| O'Hare 2002 <sup>167</sup>               | 1/1                      | 34     | HUV         | Yes                     | MG                            | 60 mg/d           | –                  | CR                    | –                                              | a few weeks                    | –           | –                                                                        |
| Wilson 2002 <sup>171</sup>               | 1/1                      | 56     | NUV         | Yes                     | B-cell non-Hodgkin's lymphoma | 20 mg/d           | –                  | CR                    | ↓JS, IM                                        | 2 weeks                        | –           | Yes                                                                      |
| Chen 2001 <sup>176</sup>                 | 1/1                      | 27     | HUVS        | Yes                     | No                            | 20 md/g           | –                  | CR                    | ↓JS                                            | –                              | –           | Yes                                                                      |
| Saeki 2001 <sup>174</sup>                | 1/1                      | 49     | HUVS        | Yes                     | No                            | 40 mg/d           | 1 year             | CR                    | ↓fever, pleural effusion, ↑RF, CT              | 1 month                        | >1          | –                                                                        |
| Ishikawa 1997 <sup>195</sup>             | 1/1                      | 33     | HUV         | Yes                     | No                            | 10 mg/d           | –                  | PI                    | –                                              | –                              | –           | Yes                                                                      |
| Wisnieski 1994, 1995 <sup>209, 210</sup> | Most/17                  | 32-76  | HUVS        | Yes                     | No                            | 20-60 mg/d        | 3 months–1.5 years | PI-CR                 | ↓OS, PS, JS, ↑RF, CT                           | 1 month                        | –           | –                                                                        |
| Martini 1994 <sup>214</sup>              | 1/1                      | 15     | HUVS        | Yes                     | No                            | 2-3 mg/kg per day | Years              | CR                    | ↓JS, OS, PS, ↑Hb                               | Rapid                          | –           | Yes                                                                      |
| Jones 1990 <sup>231</sup>                | 1/1                      | 40     | HUV         | Yes                     | No                            | 60 mg/d           | –                  | CR                    | –                                              | –                              | –           | Yes                                                                      |
| Callen 1987 <sup>239</sup>               | 16/16                    | 19-86  | –           | –                       | In some                       | 10-40 mg/d        | –                  | PI-CR                 | –                                              | –                              | –           | –                                                                        |
| Falk 1984 <sup>246</sup>                 | 1/1                      | 45     | HUV         | Yes                     | No                            | 60 mg/d           | –                  | CR                    | ↓JS, GS, ↑CT                                   | Rapid                          | –           | Yes                                                                      |
| Callen 1982 <sup>255</sup>               | 6/7                      | 2.5-66 | HUV and NUV | Yes, in some            | SLE (1)                       | 5-40 mg/d         | –                  | PI-CR                 | ↓JS in some                                    | –                              | –           | Yes, in most cases                                                       |
| Geha 1976 <sup>266</sup>                 | 1/1                      | 6      | HUV         | No                      | No                            | 2 mg/kg/d         | 6 weeks            | CR                    | ↑CT                                            | 2 weeks                        | –           | Yes                                                                      |
| OMALIZUMAB (anti-IgE)                    |                          |        |             |                         |                               |                   |                    |                       |                                                |                                |             |                                                                          |
| Gheerbrant 2017 <sup>55</sup>            | 1/1                      | 41     | HUVS        | Yes                     | No                            | 300 mg monthly    | 10 months          | PI-CR                 | –                                              | –                              | –           | –                                                                        |
| Rolls 2017 <sup>59</sup>                 | 1/1                      | 39     | NUV         | No                      | No                            | –                 | –                  | CR                    | –                                              | after 1 injection              | 16 months   | –                                                                        |
| Nucera 2017 <sup>58</sup>                | 1/1                      | 47     | HUVS        | Yes                     | No                            | 300 mg monthly    | 25 weeks           | CR <sup>15</sup>      | ↓ GS, ↑CT                                      | 2 months                       | 25 weeks    | Yes                                                                      |
| Hübner 2016 <sup>63</sup>                | 1/1                      | 72     | NUV         | No                      | No                            | 300 mq monthly    | –                  | CR                    | –                                              | –                              | –           | –                                                                        |

|                                      |       |       |                  |     |                        |                                    |                      |                  |                |                           |            |                     |
|--------------------------------------|-------|-------|------------------|-----|------------------------|------------------------------------|----------------------|------------------|----------------|---------------------------|------------|---------------------|
| Fueyo-Casado 2016 <sup>60</sup>      | 1/1   | 71    | –                | –   | No                     | 300 mg monthly                     | 23 months            | CR               | –              | 1 month                   | 23 months  | –                   |
| Ghazanfar 2015 <sup>73</sup>         | 1/1   | 68    | –                | No  | No                     | 300 mg monthly                     | 0.5 year             | CR               | –              | 1 month                   | 0.5 year   | –                   |
| Mansard 2015 <sup>70</sup>           | 2/4   | 18-82 | –                | –   | –                      | 300 mg monthly                     | –                    | CR               | –              | –                         | –          | –                   |
| Kai 2014 <sup>76</sup>               | 1/1   | –     | NUV              | –   | –                      | –                                  | 4 consecutive cycles | PI               | –              | –                         | –          | Yes                 |
| Sussman 2014 <sup>83</sup>           | 1/1   | –     | –                | –   | –                      | 150 mg every other week            | –                    | PI               | –              | –                         | –          | –                   |
| Garcia Ponce 2014 <sup>80</sup>      | 1/1   | 56    | NUV              | No  | No                     | 300 mg monthly                     | –                    | CR               | –              | after 1 injection         | –          | –                   |
| Diez 2013 <sup>87</sup>              | 3/3   | 28-54 | NUV              | No  | No                     | 150/300 mg monthly <sup>+AHS</sup> | 11-19 months         | CR               | –              | 1-4 months                | –          | Yes                 |
| Varricchi 2012 <sup>100</sup>        | 1/1   | 44    | –                | Yes | Churg-Strauss syndrome | 300 mg/d every two weeks           | 6 months             | CR <sup>IS</sup> | ↓ asthma       | after 1 injection         | –          | –                   |
| <b>DAPSONE</b>                       |       |       |                  |     |                        |                                    |                      |                  |                |                           |            |                     |
| Fadahunsi 2015 <sup>68</sup>         | 1/1   | 63    | HUVS             | –   | PsA                    | 50-100 mg/d                        | –                    | PI               | –              | –                         | –          | Yes                 |
| Alangari 2014 <sup>75</sup>          | 1/1   | 10    | NUV              | No  | No                     | 50 mg/d                            | >2months             | CR               | ↓JS, fever, IM | 1 week                    | 2 months   | Yes                 |
| McGuffin 2013 <sup>93</sup>          | 1/1   | 13    | NUV              | Yes | No                     | 100 mg/d                           | >2 years             | CR               | –              | –                         | >2 years   | –                   |
| Eliason 2010 <sup>113</sup>          | 44/58 | 21-81 | –                | –   | –                      | 25-300 mg/day                      | 4.7 months           | PI-CR            | –              | –                         | –          | No (in 23 patients) |
| Herault 2010 <sup>115</sup>          | 1/1   | 43    | HUVS             | Yes | No                     | 100 mg/d                           | –                    | PI               | –              | –                         | –          | –                   |
| Saavedra 2008 <sup>134</sup>         | 1/1   | 63    | NUV              | No  | No                     | 50 mg/d <sup>+H1AH</sup>           | >2 weeks             | CR               | –              | 2 weeks                   | –          | –                   |
| Berti 2005 <sup>157</sup>            | 1/1   | 47    | HUV              | Yes | SCLE                   | 25-50 mg/d <sup>+S</sup>           | 5 weeks              | CR               | ↑CT            | 2 weeks                   | –          | –                   |
| Leslie 2003 <sup>165</sup>           | 1/1   | 55    | –                | Yes | No                     | 100 mg/d <sup>+S</sup>             | –                    | CR               | ↓JS            | –                         | –          | –                   |
| Cadnapaphornchai 2000 <sup>181</sup> | 1/1   | 4     | HUVS             | Yes | JRA                    | 100 mg/d                           | 1 year               | CR               | ↓JS, ↑RF, CT   | –                         | 1 year     | –                   |
| Eiser 1997 <sup>194</sup>            | 1/1   | 35    | HUV              | Yes | No                     | 150 mg/d                           | –                    | CR               | ↓IM            | –                         | >2 years   | –                   |
| Cohen 1995 <sup>204</sup>            | 1/1   | 54    | HUV              | Yes | SLE                    | 50 mg/d <sup>+S</sup>              | Several months       | CR <sup>IS</sup> | –              | 1 month                   | –          | Yes                 |
| Fonseca 1992 <sup>222</sup>          | 1/1   | 37    | HUV              | Yes | No                     | 100 mg/d                           | 2.5 months           | CR               | –              | 15 days                   | 4 months   | No                  |
| Yasue 1987 <sup>237</sup>            | 1/1   | 64    | HUV              | Yes | CG                     | 75 mg/d                            | –                    | CR               | –              | –                         | –          | Yes                 |
| Fortson 1986 <sup>242</sup>          | 1/1   | 45    | HUVS             | Yes | No                     | 200 mg/d                           | –                    | CR               | ↓JS            | 1 day                     | –          | Yes                 |
| Muramatsu 1985 <sup>245</sup>        | 1/1   | 51    | NUV              | No  | No                     | 75 mg/d                            | –                    | PI               | –              | –                         | –          | –                   |
| Ruzicka 1981 <sup>257</sup>          | 1/1   | 33    | HUV              | Yes | SLE                    | 100 mg/d <sup>+S+a2a</sup>         | –                    | CR               | –              | 2 days                    | –          | Yes                 |
| <b>ETANERCEPT (anti-TNF)</b>         |       |       |                  |     |                        |                                    |                      |                  |                |                           |            |                     |
| Morgan 2009 <sup>123</sup>           | 1/1   | 43    | –                | No  | No                     | 2 mg twice weekly <sup>+S</sup>    | –                    | PI               | –              | –                         | –          | –                   |
| Krause <sup>84</sup>                 | 10/10 | >40   | HUV (1), NUV (9) | –   | –                      | 300 mg                             | Single dose          | PI               | ↓GS, JS, IM    | 16 weeks in most patients | –          | –                   |
| <b>ANAKINRA (anti-IL1)</b>           |       |       |                  |     |                        |                                    |                      |                  |                |                           |            |                     |
| Keidel 2014 <sup>78</sup>            | 1/1   | 15    | –                | Yes | UAD                    | 100 mg/d                           | 3 months             | CR               | ↓JS, GS, IM    | Immediate                 | –          | –                   |
| Botsios 2007 <sup>149</sup>          | 1/1   | 54    | NUV              | Yes | No                     | 100 mg/d                           | 13 months            | CR <sup>IS</sup> | ↓fever         | 2 weeks                   | 13 months  | Yes                 |
| <b>TOCILIZUMAB (anti-IL6R)</b>       |       |       |                  |     |                        |                                    |                      |                  |                |                           |            |                     |
| Keidel 2014 <sup>78</sup>            | 1/1   | 15    | –                | Yes | UAD                    | 8 mg/kg/month                      | –                    | CR               | ↓JS, GS, PS    | –                         | >2.5 years | –                   |
| Makol 2012 <sup>96</sup>             | 1/1   | 22    | HUV              | Yes | SLE                    | 8 mg/kg/month                      | 2 infusions          | CR <sup>IS</sup> | ↓JS, anemia,   | After 1-2                 | >12        | –                   |

|                                 |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |
|---------------------------------|-----|---------|------|-----|------------------------|--------------------------------------------------------------------------------------------------------------|---------------------|----------------------------------|----------------------|------------------------------|------------|-----|
|                                 |     |         |      |     |                        |                                                                                                              |                     |                                  | fever, ↑CT           | infusion                     | months     |     |
| <b>RITUXIMAB (anti-CD20)</b>    |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |
| Swaminath 2011 <sup>108</sup>   | 1/1 | 26      | NUV  | Yes | UC, MG                 | 1000 mg per infusion <sup>+s</sup>                                                                           | 2 cycles            | CR <sup>1s</sup>                 | ↓GS                  | –                            | >8 months  | Yes |
| Mukhtyar 2009 <sup>131</sup>    | 1/1 | 46      | NUV  | No  | No                     | 1g at fortnightly intervals <sup>+s</sup>                                                                    | 2 cycles            | CR <sup>1s</sup>                 | –                    | After first infusion         | >18 months | Yes |
| Rego 2007 <sup>146</sup>        | 1/1 | 71      | –    | No  | HCV                    | 375 mg/m <sup>2</sup> weekly                                                                                 | 4 consecutive weeks | CR                               | –                    | Fast                         | –          | –   |
| Adler 2005 <sup>156</sup>       | 1/1 | 17      | HUVS | Yes | No                     | 375 mg/m <sup>2</sup> weekly <sup>+s+MMF</sup>                                                               | 4 consecutive weeks | CR <sup>1s</sup>                 | ↓JS, ↑CT             | –                            | >6 months  | –   |
| Saigal 2003 <sup>166</sup>      | 1/1 | 40      | HUVS | Yes | SLE                    | 600 mg weekly                                                                                                | 4 weeks             | CR <sup>1s</sup>                 | –                    | Rapidly after first infusion | >4 weeks   | No  |
| Zaja 2003 <sup>163</sup>        | 1/1 | 67      | HUV  | –   | HCV                    | 375 mg/m <sup>2</sup> weekly                                                                                 | 4 weeks             | CR                               | –                    | Month                        | >30 months | –   |
| <b>INFLIXIMAB (anti-TNF)</b>    |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |
| Kroshinsky 2011 <sup>107</sup>  | 1/1 | 79      | HUVS | Yes | No                     | – <sup>+s</sup>                                                                                              | >2 years            | CR <sup>1s</sup>                 | ↓OS, PS, IM, ↑CT     | 6 weeks                      | >2.5 years | –   |
| <b>METOTREXATE</b>              |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |
| Perez 2010 <sup>120</sup>       | 3/4 | 49-63   | NUV  | –   | –                      | 7.5-15 mg weekly <sup>+s</sup>                                                                               | 3 weeks-6 months    | PI (2/3), CR (1/3) <sup>1s</sup> | –                    | 1-3 months                   | –          | –   |
| <b>CYCLOSPORINE</b>             |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |
| Fueyo-Casado 2017 <sup>60</sup> | 1/1 | 71      | –    | –   | –                      | 200 mg/d <sup>+s</sup>                                                                                       | –                   | CR                               | –                    | –                            | –          | –   |
| Tontini 2015 <sup>72</sup>      | 1/1 | 47      | HUVS | Yes | No                     | 3 mg/kg/d <sup>+s</sup>                                                                                      | –                   | PI <sup>1s</sup>                 | ↓JS                  | 2 months                     | 6 months   | –   |
| <b>RESERPINE</b>                |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |
| Demitsu 2010 <sup>117</sup>     | 7/8 | mean 55 | NUV  | –   | Sjogren's syndrome (1) | 0.3-0.4 mg/d <sup>+AHs</sup>                                                                                 | 4-8 weeks           | PI (1/7), CR (6/7)               | –                    | 4 days                       | –          | –   |
| <b>PLASMAPHERESIS</b>           |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |
| Kartal 2012 <sup>101</sup>      | 1/1 | 35      | NUV  | No  | No                     | Two plasma exchanges 6 months apart                                                                          | 6 months            | CR                               | –                    | –                            | –          | Yes |
| Grimbert 2001 <sup>173</sup>    | 1/1 | 36      | HUVS | Yes | No                     | –                                                                                                            | Three sessions      | CR                               | ↓fever, NS, ↑CT      | 24 hours after last session  | –          | –   |
| <b>CYCLOPHOSPHAMIDE</b>         |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |
| Hauser 2017 <sup>61</sup>       | 1/1 | 24      | HUV  | Yes | No                     | 15 mg/kg <sup>+s</sup>                                                                                       | –                   | CR                               | ↓GS, OS, JS, IM, ↑CT | After 6 courses              | –          | –   |
| Alachkar 2007 <sup>142</sup>    | 1/1 | 53      | HUVS | Yes | No                     | 500 mg every two weeks <sup>+s</sup>                                                                         | 9 months            | PI                               | ↑RF, CT              | –                            | –          | –   |
| Worm 1998 <sup>185</sup>        | 2/2 | 43-45   | HUV  | Yes | No                     | 500 mg i.v. on day 1 and 50 mg oral between the pulses. The pulses were repeated every 2 weeks <sup>+s</sup> | 16 pulses           | CR                               | ↓OS, JS, CICs, ↑CT   | After the tenth pulse        | –          | –   |
| <b>INDOMETHACIN</b>             |     |         |      |     |                        |                                                                                                              |                     |                                  |                      |                              |            |     |

|                                          |      |       |                     |     |                         |                                                   |             |                                     |                       |               |             |     |
|------------------------------------------|------|-------|---------------------|-----|-------------------------|---------------------------------------------------|-------------|-------------------------------------|-----------------------|---------------|-------------|-----|
| Bisaccia 1988 <sup>235</sup>             | 1/1  | 30    | HUV                 | Yes | SLE, AIT                | 25 mg four times a day <sup>+AHs</sup>            | –           | CR                                  | –                     | –             | –           | Yes |
| Millns 1980 <sup>260</sup>               | 9/10 | >16   | HUV (1),<br>NUV (8) | Yes | No                      | 25 mg twice times daily to 50 mg four times daily | 1-21 months | PI (3/9),<br>CR (6/9)               | ↓JS, GS, PS (in some) | 17 days       | –           | Yes |
| <b>MYCOPHENOLATE MOFETIL</b>             |      |       |                     |     |                         |                                                   |             |                                     |                       |               |             |     |
| Grotz 2009 <sup>121</sup>                | 1/1  | 72    | HUVS                | Yes | No                      | 2 g/d <sup>+s</sup>                               | Short term  | CR                                  | –                     | Swiftly       | >2 years    | –   |
| Pisoni 2005 <sup>160</sup>               | 1/1  | 50    | –                   | Yes | SLE                     | 2 g/d                                             | 32 months   | PI                                  | –                     | 2 months      | –           | –   |
| Thorne 2002 <sup>169</sup>               | 1/1  | 67    | HUV                 | Yes | No                      | 30 mg/kg/d <sup>+s</sup>                          | –           | CR                                  | ↓OS                   | 6 months      | 10 months   | –   |
| Worm 2000 <sup>186</sup>                 | 2/2  | 44-45 | HUV                 | Yes | No                      | 2 g/d                                             | >15 months  | CR                                  | ↓OS, JS, ↑CT          | –             | >15 months  | No  |
| Ghadban 2008 <sup>136</sup>              | 1/1  | 48    | HUVS                | Yes | No                      | 1-1.5 g/d <sup>+cp+s</sup>                        | 18 months   | CR <sup>is</sup>                    | ↓OS, JS, ↑CT          | –             | 18 months   | –   |
| <b>COLCHICINE</b>                        |      |       |                     |     |                         |                                                   |             |                                     |                       |               |             |     |
| Jimenez Ferrera 2013 <sup>90</sup>       | 1/1  | 40    | NUV                 | No  | No                      | 1 mg/d <sup>+s</sup>                              | >1 month    | CR <sup>is</sup>                    | –                     | 1 month       | –           | –   |
| Ashida 2013 <sup>94</sup>                | 1/1  | 75    | HUV                 | No  | No                      | 1 mg/d <sup>+s</sup>                              | –           | PI <sup>is</sup>                    | –                     | 1 week        | –           | –   |
| Mukkamala 1996 <sup>199</sup>            | 1/1  | 36    | HUV                 | Yes | No                      | 0.6 mg twice/d <sup>+s</sup>                      | 2 months    | CR <sup>is</sup>                    | –                     | 1 week        | –           | –   |
| Asherson 1991 <sup>225</sup>             | 1/1  | 47    | NUV                 | Yes | No                      | 0.5 mg/d                                          | 30 months   | CR                                  | –                     | 10-14 days    | 30 months   | –   |
| Callen 1987 <sup>239</sup>               | 1/2  | 19-86 | –                   | –   | In some                 | 0.6 mg/bid <sup>+s</sup>                          | –           | PI <sup>is</sup>                    | –                     | –             | –           | –   |
| Werni 1986 <sup>243</sup>                | 1/1  | 72    | HUV                 | Yes | No                      | 0.5 mg three times per day                        | >8 months   | CR                                  | ↓fever, JS, GS        | 3 days        | >8 months   | Yes |
| Muramatsu 1985 <sup>245</sup>            | 1/1  | 51    | NUV                 | No  | No                      | 1 mg/d                                            | –           | CR                                  | –                     | A few days    | –           | –   |
| Wiles 1985 <sup>244</sup>                | 2/2  | 30-68 | NUV (1),<br>HUV (1) | Yes | No                      | 0.6 mg twice-three times a day                    | 5-8 months  | CR <sup>is</sup>                    | –                     | Rapid         | –           | Yes |
| Newton 1984 <sup>248</sup>               | 1/1  | 61    | NUV                 | No  | IBD                     | 0.25 mg three times a day                         | 6 months    | CR                                  | –                     | –             | –           | –   |
| <b>HYDROXYCHLOROQUINE</b>                |      |       |                     |     |                         |                                                   |             |                                     |                       |               |             |     |
| Calistru 2010 <sup>114</sup>             | 1/1  | 56    | HUV                 | Yes | MCTD                    | 400 mg/d                                          | 1 year      | CR <sup>is</sup>                    | ↓JS                   | –             | 1 year      | –   |
| Farkas 2001 <sup>178</sup>               | 1/1  | 40    | HUV                 | Yes | Acquired C1q-deficiency | 200-400 mg/d                                      | –           | –                                   | ↓OS                   | 3 months      | A few years | –   |
| Werder 1997 <sup>193</sup>               | 1/1  | 45    | HUV                 | Yes | No                      | 100 mg/d                                          | –           | CR <sup>is</sup>                    | ↓OS, PS, JS           | –             | –           | –   |
| Wisniewski 1995 <sup>210</sup>           | 3/3  | >31   | HUVS                | Yes | No                      | 200 mg twice daily <sup>+s</sup>                  | 1 year      | PI (1/3),<br>CR (2/3) <sup>is</sup> | ↑CT                   | –             | –           | –   |
| Lopez 1984 <sup>247</sup>                | 1/1  | 31    | HUVS                | Yes | No                      | 200 mg twice daily                                | 1-2 years   | CR                                  | ↓JS                   | –             | –           | Yes |
| <b>INTRAVENOUS IMMUNOGLOBULINS</b>       |      |       |                     |     |                         |                                                   |             |                                     |                       |               |             |     |
| Fujimoto 2012 <sup>97</sup>              | 1/1  | 31    | HUV                 | Yes | –                       | 400 mg/kg/d <sup>+s</sup> ,<br>DP, MMF            | 5 days      | CR                                  | ↓JS                   | –             | –           | –   |
| Yamazaki-Nakashimada 2009 <sup>127</sup> | 1/1  | 4     | HUV                 | Yes | SLE                     | 1 g/kg/d <sup>+s</sup>                            | –           | PI                                  | ↓GS, OS               | 24 hours      | –           | –   |
| Staubach-Renz 2007 <sup>144</sup>        | 1/1  | 37    | HUVS                | Yes | No                      | 2 g/kg/d                                          | –           | CR                                  | ↓GS, OS               | After 1 cycle | –           | Yes |

|                                     |     |     |      |     |                      |                                                |             |                  |              |                             |   |     |
|-------------------------------------|-----|-----|------|-----|----------------------|------------------------------------------------|-------------|------------------|--------------|-----------------------------|---|-----|
| Wisnieski 1994 <sup>209</sup>       | 1/1 | 31  | HUVS | Yes | No                   | 50 mg infusion given every other day for days  | 3 cycles    | PI               | ↓JS, OS, ↑RF | after first treatment cycle | – | Yes |
| <b>PENTOXIFYLLINE +DAPSONE</b>      |     |     |      |     |                      |                                                |             |                  |              |                             |   |     |
| Nürnberg 1994 <sup>211</sup>        | 1/1 | 40  | HUVS | Yes | No                   | 1200mg+100mg per day                           | 16 months   | CR               | ↓OS, JS, GS  | 2 weeks                     | – | –   |
| Christiansen 2015 <sup>69</sup>     | 1/1 | 71  | NUV  | No  | Acquired haemophilia | 100 mg/d <sup>+/-s</sup> , dapsone, colchicine | A few weeks | CR               | –            | A few weeks                 | – | –   |
| Callen 1987 <sup>239</sup>          | 1/1 | >18 | –    | –   | In some              | 150 mg/d <sup>+s</sup>                         | –           | PI <sup>1s</sup> | –            | –                           | – | –   |
| <b>CLARITHROMYCIN</b>               |     |     |      |     |                      |                                                |             |                  |              |                             |   |     |
| Diplomatico 2017 <sup>39</sup>      | 1/1 | 17  | NUV  | Yes | SLE, Graves' disease | 15 mg/kg/d                                     | 21 day      | CR               | –            | Rapidly                     | – | No  |
| Handfield-Jones 1991 <sup>229</sup> | 1/1 | 45  | HUV  | Yes | No                   | 10 mg weekly i.m.                              | 6 months    | CR               | ↓ JS         | 1 month                     | – | Yes |
| <b>IVIG+AZA</b>                     |     |     |      |     |                      |                                                |             |                  |              |                             |   |     |
| Breda 2013 <sup>91</sup>            | 1/1 | 16  | HUVS | Yes | No                   | 1 g/kg/dose+100 mg/d <sup>+s</sup>             | >18 months  | CR <sup>1s</sup> | –            | 18 months                   | – | –   |

–: no data or not defined in the paper; UV: urticarial vasculitis; HUV: hypocomplementemic urticarial vasculitis; HUVS: hypocomplementemic urticarial vasculitis syndrome; CR: complete cutaneous remission; PI: partial cutaneous improvement; <sup>1s</sup> allowed to taper the dose of steroids and/or discontinuance of steroids; <sup>+s</sup> add-on therapy to steroids; <sup>+AHS</sup> add-on therapy to antihistamines; <sup>+cp</sup> cyclophosphamide was added; <sup>+mmf</sup> mycophenolate mofetil was added; MG: monoclonal gammopathy; JRA: juvenile rheumatoid arthritis; CG: cryoglobulinemia; PsA: psoriatic arthritis; SCL: subacute cutaneous lupus erythematosus; IL: interleukin; UAD: undifferentiated autoimmune disorder; UC: ulcerative colitis TNF: tumor necrosis factor; IBD: inflammatory bowel disease; ↓/↑: decrease (normalization) or increase of symptoms (parameters); JS: joint symptoms (arthralgia/arthritis); IM: inflammatory markers (e.g. ESR, CRP); OS: ocular symptoms (e.g. uveitis); PS: pulmonary symptoms (e.g. cough); Hb: hemoglobin; GS: gastrointestinal symptoms (e.g. abdominal pain); RF: renal function; CT: complement components; GS: general symptoms (e.g. malaise); CICs: circulating immune complexes; AZA: azathioprine; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; NS: neurological symptoms; HCV: hepatitis C infection; AIT: autoimmune thyroiditis; NSAIDs: nonsteroidal anti-inflammatory drugs

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