

Expert Opinion

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Anti-inflammatory

Emerging drugs for chronic urticaria

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Chronic urticaria (CU), with or without angioedema, is a frequent disorder defined as the occurrence of pruritic wheals for > 6 weeks. Studies carried out in the last two decades showed that the origin of the disease is autoimmune in up to 50% of cases. Currently available treatments include antihistamines, corticosteroids and ciclosporin; recently, leukotriene receptor antagonists proved effective in a subset of patients as well. For patients with an unremitting and extremely severe disease unresponsive to standard treatments, plasmapheresis and immunosuppressive drugs have been successfully attempted. Recent findings that the autologous plasma skin test scores positive in nearly all patients and that plasmas from patients with both autoimmune and 'idiopathic' chronic urticaria are frequently characterised by signs of thrombin activation (plasma levels of prothrombin fragment F_{1.2} are significantly increased) suggest that clotting cascade might be somehow involved in the pathogenesis of CU. These findings put under a new light some rather sparse studies of the effect of drugs active on the coagulation system (heparin and oral anticoagulants) in patients with CU.

Keywords: anticoagulants, chronic urticaria, heparin, therapy

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1. Background

Chronic urticaria (CU) is a common skin disorder characterised by the recurrent occurrence of short-lived wheals accompanied by redness and itching for > 6 weeks. Wheal size may range from a few millimetres to several centimetres. At least 50% of patients with CU have also angioedema [1], a lesion that can be defined as a transient subcutaneous and/or submucosal oedema. It has been estimated that this disease affects about 0.1% of the general population [2], but the real prevalence possibly exceeds this figure [3]. CU occurs predominantly in adults; women are more commonly affected than men [4,5], and the disease frequently shows a familial pattern [6]. It is an extremely distressing disorder, causing relevant personal, domestic and social disability and a marked worsening in quality of life [7,8].

CU has long been considered as a 'mysterious' disorder. Not long ago CU was still frequently ascribed to anxiety or to intolerance to foods, food dyes or food additives [2,3,9]; as a consequence, for years CU patients have been prescribed 'hypoallergenic' diets, causing much discomfort and exerting little or no benefit [10-12]. Nowadays, it is clear that food allergy/intolerance underlies CU at best in a very small proportion of patients and that dietary restrictions are most often useless. The last 20 years have finally recorded substantial advances in our understanding of the pathogenesis of this disease. In 1986 Grattan *et al.* observed for the first time that the intradermal injection of autologous serum induced a wheal and flare reaction in a significant proportion of patients with CU [13]. After a couple of years Gruber *et al.* demonstrated the presence of nonfunctional circulating anti-IgE IgG autoantibodies by immunoassay in three out of six patients with CU and five out of nine patients with cold urticaria [14]. Nonfunctional anti-IgE was subsequently found in many patients with

atopic syndromes and healthy controls. The first report of functional autoantibodies with properties of anti-IgE in CU was published by Grattan *et al.* in 1991 [15], and the work was subsequently extended by the same group to define that the main serological mediator of whealing is an autoantibody directed against the α -subunit of the high-affinity IgE receptor (Fc ϵ RI α), which can be detected in about 25% of CU patients [16], an observation that was confirmed also by independent researchers [17,18]. It was finally established that anti-IgE autoantibodies can be detected only in about 5% of cases [2]. Both anti-Fc ϵ RI α and anti-IgE autoantibodies are able to cause direct crosslinking of adjacent Fc ϵ RI receptors, thus inducing mast cell activation and release of inflammatory mediators. In addition, the monovalent combination of autoantibodies and receptors causes complement activation and generation of anaphylatoxins. Recent studies by Kaplan and his group demonstrated that in CU, histamine release from mast cells is complement dependent [19] and that C5a enhances IgG-dependent histamine release from these cells [20].

It has been recently observed that urticaria is characterised by relevant inflammatory aspects. Sites of whealing show a perivascular infiltration of lymphocytes (mainly CD4⁺), monocytes, neutrophils and eosinophils, a picture recalling the late-phase antigen-induced reaction [21,22]. Moreover, Wedi *et al.* [23] observed *de novo* generation of leukotriene C₄ (LTC₄), an arachidonic acid derivative, by normal basophils stimulated with sera from CU patients; as LTC₄ induces a wheal-and-flare reaction on intradermal injection in humans, this substance has now to be included among mediators of urticaria. Other mediators of inflammation processes such as platelet-activating factors, several cytokines and several chemokines are released by activated mast cells [24,25], but their relevance in the pathogenesis of urticaria lesions is still undefined.

2. Medical need

A routine assay able to detect patients with functional anti-Fc ϵ RI α and/or anti-IgE autoantibodies is still lacking. *In vitro* histamine-release assays using either basophils or mast cells from normal donors to be stimulated with patients' sera show much variability, are time consuming, and can be carried out only in selected centres. The autologous serum skin test (ASST) has been recently adopted as a readily available alternative test *in vivo*, although several aspects are still poorly defined. Asero's group have shown that ASST elicits a wheal-and-flare reaction in ~ 50% of CU patients, but sera from only a proportion of those who are ASST-positive are able to induce histamine release from cultured human basophils from one normal donor [26]. The group demonstrated that the histamine-releasing activity *in vitro* is associated with the serum fraction > 100 kDa, and hence probably with functionally active IgG autoantibodies for the high-affinity IgE receptor [26,27]. Very recently, this discrepancy was partially cleared, as it was shown that sera from virtually all patients with CU who score strongly positive on ASST

(notably, a selected subset of patients with CU) are able to induce significant histamine release from basophils and mast cells, provided that cells from several different donors are employed [28]. Several aspects remain contradictory however. For instance, Fagiolo and colleagues have demonstrated that sera from CU-containing anti-Fc ϵ RI autoantibodies retain their ability to induce a wheal-and-flare reaction *in vivo* also after depletion of IgG [29], a finding that clearly puts the role played by autoantibodies in intradermal testing into question, at least in part. Moreover, it is generally accepted that anti-Fc ϵ RI autoantibodies can be detected in no more than 20 – 30% of CU patients [2,27]. All these data point to the fact that histamine-releasing factors other than anti-Fc ϵ RI or anti-IgE autoantibodies might be involved in the pathogenesis of the disorder and might account for the discrepancy between the results of *in vitro* and *in vivo* assays. Some years ago, Kermani *et al.* [30] reported the preliminary, partial characterisation of a histamine-releasing factor with a molecular weight > 30 kDa, and a histamine-releasing factor possibly involved in CU was described also by Claveau *et al.* [31]; however, no report of further characterisation of these factors has appeared in recent years in the medical literature.

One interesting aspect that is gradually emerging from ongoing studies of CU is the discrepancy between ASST and skin testing with autologous plasma (APST) anticoagulated with sodium citrate. Whereas the former, as reported above, scores positive in ~ 50% of cases, the latter is positive in ~ 90% of patients (and negative in normal controls). Because serum and plasma do not differ in their autoantibody content, this observation points to a possible role of clotting factors in the wheal-and-flare reactions induced by autologous plasma. In effect, very recent *in vitro* studies showed that plasmas from CU patients show significantly higher levels of prothrombin fragment F₁₊₂, a polypeptide of about 34 kDa that is released into the circulation during the activation of prothrombin to thrombin by Factor Xa [32]. This finding opens new insights into possible therapeutic strategies for this disease and also explains the reportedly good results obtained in some patients with drugs active on the coagulation system (see below).

3. Existing treatment and therapeutic class review

The treatment of CU does not differ in patients with autoimmune/autoreactive (i.e., positive on ASST with or without demonstrable histamine-releasing activity *in vitro*, respectively) or idiopathic (i.e., negative both on ASST and *in vitro*) disease.

Although extremely distressing and causing marked worsening in quality of life, the prognosis *quoad vitam* and *quoad valitudinem* of CU is excellent. Thus, it is not surprising that the main objective of current treatment strategies is primarily to control symptoms with the least toxic drugs such as antihistamines and leukotriene receptor antagonists. Drugs that interfere with the immune system are given only in those

Table 1. Anti-H₁-antihistamines for systemic use presently available on the Italian market.

Drug	Producer	Administration	Dose/administration
Hydroxyzine	UCB Pharma	p.o., b.i.d. i.m. or i.v.	25 mg 100 mg
Prometazine	Pharmacia Pfizer	i.m. or i.v. p.o., b.i.d.	50 mg 25 mg
Chlorfenamine	Schering-Plough	p.o., b.i.d. i.m. or i.v.	8 mg 10 mg
Oxatomide	Formenti	p.o., b.i.d.	30 mg
Ketotifen	Innovex	p.o., b.i.d.	2 mg (suspension 0.2 mg/ml)
Fexofenadine	Caber	p.o., once daily	120 – 180 mg
Loratadine	Schering-Plough Essex Italia Firma	p.o., once daily	10 mg
Desloratadine	Schering-Plough	p.o., once daily	5 mg
Cetirizine	UCB Pharma Lusofarmaco Mediolanum	p.o., once daily	10 mg
Levocetirizine	UCB Pharma	p.o., once daily	5 mg
Mizolastine	Sanofi-Synthelabo	p.o., once daily	10 mg
Ebastine	Almirall Chiesi	p.o., once daily	10 – 20 mg

(fortunately rather unusual) patients that do not respond to first-line drugs. A number of drug classes belong to this group.

3.1 Antihistamines

Because histamine is unquestionably the main mediator of urticaria, the first-line treatment in all CU patients is represented by H₁-receptor antagonists [33]. A classification of the main antihistamines presently available on the Italian market is shown in Table 1. Today there is a tendency to avoid older sedating antihistamines and use the newer low-sedating drugs such as cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, ebastine and mizolastine. In the authors' experience, all these drugs at the daily doses recommended (see Table 1) are able to control pruritus and wheals in the large majority (at least 90%) of urticaria patients [34-39]. Although some comparative studies suggest that cetirizine is the most effective among this group of drugs [40], there is a bulk of randomised-controlled studies showing that all nonsedating antihistamines can be employed in CU with good results (reviewed in [41]). At the beginning of treatment antihistamines should be taken on a regular basis rather than on demand to maximise benefit. Older sedating drugs such as hydroxyzine, diphenhydramine or the tricyclic antihistamine doxepin are indicated in a single nocturnal dose in selected patients complaining of severe pruritus during the night [2,9,42]. Based on the extremely low toxicity of the newer nonsedating antihistamines, some authors suggest increasing the dosage off-label in patients not responding to the usual recommended doses in order to gain a better control of the

disease [2,9,41,43]. Evidence supporting this approach is sparse, and well-performed double-blind, placebo-controlled studies comparing normal and off-label doses are missing. In the authors' experience, only a small proportion of patients who do not respond satisfactorily to usual doses of antihistamines respond to two to four times higher doses of the same drugs.

The role of H₂-receptor antagonists in combination with H₁-receptor antagonists in CU patients [44] is still controversial. This pharmacological combination was originally proposed after it was found that ~ 15% of total histamine receptors in the skin are of the H₂ type. Although some controlled studies have shown that H₂-receptor antagonists may provide statistically significant benefit if they are added to H₁-receptor antagonists [44-46], in the authors' hands the combined H₁- and H₂-antagonists therapy gives little benefit over anti-H₁ therapy alone.

3.2 Leukotriene receptor antagonists

Peptide leukotrienes are potent mediators of inflammatory processes derived from arachidonic acid through the 5-lipoxygenase pathway and produced by several cell types [47]. There is some evidence that peptide leukotrienes may act as mediators in urticaria. Wedi *et al.* [23] showed that sera from CU patients elicit *de novo* synthesis of peptide leukotrienes by basophils of normal donors. Furthermore, the intradermal injection of peptide leukotrienes (LTC₄, -D₄ and -E₄) elicits a wheal-and-flare reaction either in CU patients or in normal subjects [48], and, on a molar basis, peptide leukotrienes are 100-times more potent than histamine in inducing

wheal-and-flare reactions, but without itching. Finally, human mast cells synthesise and release peptide leukotrienes following IgE-mediated stimulation *in vitro* and it is reasonable to suppose that the same may occur *in vivo* following stimulation by anti-FcεRI or anti-IgE autoantibodies. Based on all these observations a clinically relevant role for leukotrienes has been suggested in CU patients not responding to antihistamine therapy. After the appearance of some anecdotal reports suggesting that leukotriene receptor antagonists may be beneficial in some patients with CU [49-53] and in some cases of delayed pressure urticaria [54], the superiority of these drugs over placebo in CU has been established in some controlled studies [55-58]. It must be noted, however, that most studies have shown a beneficial effect of leukotriene antagonists, either montelukast or zafirlukast, when used in combination with H₁-antihistamines and not as monotherapy [59]. Furthermore, one controlled study failed to show a substantial advantage of the combined therapy of desloratadine plus montelukast with respect to desloratadine as monotherapy in patients affected by moderate CU [60]. The overall impression is that it may be worth trying leukotriene antagonists in CU patients whose urticaria is not adequately controlled by antihistamines alone, although the subset of patients who can benefit from leukotriene antagonist administration has not been clearly identified as yet. Bagenstose *et al.* reported that zafirlukast improves CU control when added to cetirizine in patients positive on ASST [58], and Sanada *et al.* showed that the patients for whom montelukast was effective were younger and their duration of illness shorter [61]; in the experience of Asero and Tedeschi, leukotriene receptor antagonists were able to a control CU in a proportion of patients who did not respond to antihistamines [62], and were in some cases useful to prevent NSAID-induced exacerbations of the disease [63]. As pathogenic mechanisms of urticaria may differ between different subsets of CU patients, it is possible that the clinical response to leukotriene receptor antagonists is variable. Two leukotriene receptor antagonists are presently available in Italy for asthma treatment: montelukast, 5- and 10-mg tablets, and zafirlukast. These drugs are given at doses of 10 mg once a day and 20 mg b.i.d.

The 5-lipoxygenase blocker zileuton, which inhibits peptide-leukotriene generation, has also been employed with success in the treatment of CU [50]; this drug is presently not available in Italy as well as in many other countries, and experience with this substance is, therefore, limited.

In conclusion, although treatment of CU with leukotriene receptor antagonists is still lacking a strong, unequivocal (level A) evidence, these drugs 'are safe and are worth trying', as recently suggested in an authoritative review article [9].

3.3 Corticosteroids

Although they are widely used as the second-line drug of choice in patients who do not respond to antihistamines, a search of MEDLINE and EMBASE found no study assessing the efficacy of corticosteroids in CU. Nonetheless, the efficacy

of steroid therapy is unquestionably high, although long-term treatments are hampered by the known side effects, including diabetes, hypertension, osteoporosis and gastrointestinal bleeding. Short courses of systemic steroids (for example, prednisone 25 mg/day or methylprednisolone 16 mg/day to be tapered and withdrawn within 7 – 14 days) can be prescribed in severe cases. This approach is frequently sufficient to induce a partial remission of the disease that so becomes responsive to antihistamines. In some cases, oral steroid therapy can be prolonged, but it has to be kept at the lowest effective dose (for example, prednisone 5 mg/day or every other day).

3.4 Ciclosporin

In patients with severe, unremitting urticaria that does not respond to antihistamines and relapses whenever corticosteroids are tapered down, ciclosporin represents a viable alternative. Ciclosporin is an immunosuppressive and anti-inflammatory drug currently employed to avoid graft rejection in transplanted patients and to treat some autoimmune disorders. It rapidly inhibits the release of histamine as well as of LTC₄ and prostaglandin D₂ from immunologically activated basophils and skin mast cells [64]. Oral ciclosporin was found to be effective in patients with severe unremitting urticaria and a poor response to conventional treatment with H₁-antihistamines [65], an observation that was subsequently confirmed by some controlled studies [66,67]. More recently, Grattan *et al.* carried out a randomised, double-blind, placebo-controlled study of ciclosporin in CU; 8 of 19 patients receiving ciclosporin 4 mg kg⁻¹/day versus none of the patients receiving placebo had a remission of the disease associated with a reduction in serum histamine-releasing activity [68]; in most cases treated patients showed evidence of circulating histamine-releasing autoantibodies both *in vitro* and *in vivo*. Altogether, > 75% of patients with unremitting urticaria show an excellent response to ciclosporin [67]. However, ciclosporin has potentially severe side effects and its use should be limited to selected patients.

3.5 Other immunosuppressive treatments

3.5.1 Methotrexate

Low-dose methotrexate was effective in two patients with autoantibody negative CU refractory to conventional therapies [69]. So far, however, the experience with this drug is very limited and its clinical use should be considered only in patients with severe, unremitting steroid-dependent CU.

3.5.2 Cyclophosphamide

Recently, two case reports showed the efficacy of low-dose cyclophosphamide in CU patients. In the first one [70], the drug was given intravenously as a pulse therapy; although effective, such a regimen is time consuming and requires adequate facilities. In the second study [71], the drug was given orally to a patient with a steroid-dependent ciclosporin-resistant CU at a dose of 100 mg (corresponding to 1.5 mg/kg body weight) for 5 days/week, associated with acetylcysteine

600 mg/day to reduce bladder toxicity, with excellent results. The drug was given at the planned dose for 1 year before being gradually reduced. Although this alkylating agent has a number of potentially severe side effects, the patient did not experience any adverse drug reaction, probably due to the fact that the dose used (2000 mg/month) was much lower than that normally employed to treat malignancies.

3.5.3 High-dose intravenous immunoglobulin

High-dose intravenous immunoglobulin (IVIG) is extensively used to treat several immune-mediated diseases, including vasculitis, connective-tissue disorders, steroid-dependent bronchial asthma and myocarditis [72]. IVIG exerts a complex immunomodulating effect, resulting in immunosuppression [73]. The rationale for their use in CU stems from the observation that the disease is autoimmune in a significant proportion of patients. In the study by O'Donnell *et al.* [74], 9 out of 10 patients (in most cases showing evidence of circulating, histamine-releasing autoantibodies, both *in vivo* and *in vitro*) responded well to IVIG; 3 of them were still in remission 3 years after the treatment, 2 had temporary complete remissions, and 4 improved. However, in a subsequent study IVIG induced only temporary remissions of the disease or did not exert any appreciable effect [75]. Altogether, the role of IVIG in CU is still undefined, and this approach seems not sufficiently cost effective to be suggested as a routine therapeutic option.

3.6 Plasmapheresis

Again, based on the autoimmune origin of a proportion of cases, some patients with severe autoimmune CU have undergone plasmapheresis [76]. Although the treatment proved effective, this approach cannot be suggested for routine long-term management of CU patients.

3.7 Other immunomodulators

3.7.1 Hydroxychloroquine

The first report of a beneficial effect of hydroxychloroquine in patients with urticarial vasculitis appeared a long time ago [77]. More recently, the drug, when added to standard therapies, was found to exert some beneficial effects in patients with refractory CU in an open-label study [78] and in a randomised placebo-controlled study [79]. However, both studies showed several pitfalls: in the latter one, by comparison with controls, patients' quality of life significantly increased, but this was not associated with a reduction of urticaria score and of medication requirement. The observation is nonetheless interesting in view of previous observations that hydroxychloroquine inhibits histamine release, basophil CD63 expression and *de novo* production of leukotrienes by cultured basophils stimulated with sera from ASST-positive patients [23].

3.7.2 Sulfasalazine and dapsone

Some case reports have suggested the efficacy of two immunomodulatory drugs, sulfasalazine [80,81] and dapsone [82],

in CU. Interestingly, dapsone shows the same *in vitro* properties as hydroxychloroquine on cultured, stimulated human basophils [23]. Experience with these drugs is, however, very limited, and their routine use cannot be recommended.

3.7.3 Tacrolimus

In a recent open study on 19 patients with severe CU, 70% of subjects responded to low-dose tacrolimus; 9 patients were able to discontinue antihistamines (and in 2 cases corticosteroids as well). The effect lasted for 3 months in 60% of responders [83].

3.8 Levothyroxine

Some researchers reported that levothyroxine was effective in some patients with CU and thyroid autoimmunity, but this observation has not been confirmed by others [84,85]. The authors' opinion is that this drug should be considered in addition to standard therapies only in patients with both hypothyroidism and CU.

3.9 Anabolising agents: stanozolol

Stanozolol, which is widely employed in the preventive treatment of hereditary angioedema, has been used with good results in a case of steroid-dependent CU several years ago [86]. Although stanozolol exerts a number of regulatory effects on inflammatory processes, the clinical experience is limited and this drug cannot be recommended for the usual therapeutic approach to the CU patient.

4. Current research goals

As mentioned before, one novelty emerging from the authors' current studies is that nearly all CU patients are positive on intradermal testing with autologous plasma anticoagulated with sodium citrate; moreover, CU patients show significantly increased plasma levels of prothrombin fragment F_{1.2}. These findings suggest that the clotting cascade might be somehow involved in the pathogenesis of CU and are in keeping with the observation by Fagiolo *et al.* [29] that CU sera depleted of anti-FcεRI and anti-IgE IgG autoantibodies still maintain their ability to induce a wheal-and-flare reaction on ASST. In other words, a positive ASST would not be (or would be only partially) the result of the presence of circulating autoantibodies, which in turn are essential for histamine release on *in vitro* assays. These findings, although preliminary and needing a better definition, open new insights into possible therapeutic strategies for CU.

5. Scientific rationale

These observations put under a new light some rather sparse studies of the effect of drugs active on the coagulation system in patients with CU. Such potential therapeutic agents, along with the scientific rationale for their use in patients with CU, are discussed in this section.

5.1 Heparin

Some recent studies clearly showed that heparin exerts a profound inhibitory effect both on skin response to autologous serum [26,87] and on histamine release from human cultured basophils *in vitro* [26]. Given that in those studies the *in vivo* effect of heparin was immediate, it seems unlikely that this is due to an interference with the intracellular system of second messengers [87]; a direct effect at a cellular level or a direct binding of circulating histamine-releasing factors seem more likely explanations for this observation. Importantly, heparin exerts its inhibitory effect *in vivo* also in ASST-positive patients whose sera are not able to induce any histamine release *in vitro* (i.e., do not contain anti-FcεRI or anti-IgE autoantibodies), but does not inhibit the wheal-and-flare reaction induced by a skin prick test with histamine or with a specific allergen extract in allergic subjects [26]. These observations seem to suggest that histamine is not the target of heparin, at least *in vivo*. *In vitro*, heparin is able to inhibit basophil histamine release induced by different agents such as anti-IgE, formyl-methionyl-leucyl-phenylalanine and IL-3, all of which interact with distinct receptors and activate basophils via various pathways. The inhibitory effect of heparin is dose dependent [26]. These findings are in keeping with previous findings of the inhibitory effects of heparin on histamine release from both basophils and mast cells of asthmatic patients [88,89].

Besides its well-known anticoagulant activities, heparin is able to interact with a number of plasma proteins and mast cell surface components [90]. No effect of heparin on antigen–antibody interaction would be theoretically expected.

In the clinical practice, systemic heparin administration inhibits IgE-mediated response to antigen in both the skin and lung of allergic subjects [91], and a case of CU responding to the subcutaneous administration of heparin sodium (5000 U b.i.d.) has been very recently reported [92].

5.2 Oral anticoagulants

The beneficial effect of the oral anticoagulant warfarin was first observed in single case reports [93,94], but was dismissed by a subsequent study [95]. The efficacy of warfarin in a proportion of patients was finally established by a double-blind, placebo-controlled crossover study [96]; interestingly, all responders in that study were negative on ASST, and the effects of the drug were not associated with a modification of responses to histamine and other mast cell mediators responsible for the acute wheal-and-flare. Warfarin inhibits the synthesis of vitamin K-dependent proteins in the clotting cascade (i.e., prothrombin, and factors VII, IX and X) acting as a

competitive inhibitor of the vitamin that prevents its conversion from the inactive to the active form. Warfarin inhibition of thrombin production produces also anti-inflammatory effects, as thrombin induces secretion of adhesion molecules (E-selectin and IL-8), which facilitate neutrophil activation and extravasation [97]. The relevance of expression of adhesion molecules in the early phases of CU and delayed pressure urticaria can be now appreciated also in the light of a study carried out some 30 years ago showing the efficacy of trasylol, a kallikrein inhibitor, in CU [98]. It is, therefore, possible that warfarin downregulates some adhesion molecules that are relevant in the pathogenesis of CU.

6. Expert opinion

One has to admit that the current treatment of CU, although very, or at least sufficiently, effective in the large majority of patients, is not totally satisfying. The drugs we presently use as a first-line treatment block specific receptors for pro-inflammatory substances, such as histamine and leukotrienes, whereas second-line drugs act by downregulating at different levels the synthesis and release of mediators of inflammation (including histamine, cytokines, and chemokines) from effector cells. Immunosuppressive drugs, such as ciclosporin and probably tacrolimus, are very effective in most CU patients, but their potential toxicity limits a wide clinical employment. So far, our incomplete understanding of the pathogenesis of CU has hampered the search for new low-toxicity active drugs. An autoimmune process can be detected only in a minority of patients, and even in these subjects autoantibodies seem unable to explain all the phenomena that characterise this disease. The ASST is positive in ~ 50% of patients; such proportion includes all those showing an autoimmune process, but also subjects whose sera do not seem to contain autoantibodies. Finally, the APST is positive in ~ 90 – 95% of patients with CU [32]. The picture that is gradually emerging from the most recent studies suggests that CU is not exclusively an autoimmune disorder and that the clotting cascade might play a relevant role in the disease. Although some reports show that drugs able to interfere at different levels with the coagulation system may be effective in some patients with CU, further studies are urgently needed to identify more precisely what finally causes the activation of prothrombin and how the coagulation cascade participates in the mechanism of the disease. The results of these studies will probably represent the starting point for the development of new therapeutic approaches to this often disabling disease.

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