

REVIEW ARTICLE

Schnitzler's syndrome: diagnosis, treatment, and follow-up

A. Simon¹, B. Asli², M. Braun-Falco³, H. De Koning⁴, J.-P. Fermanand², C. Grattan⁵, K. Krause⁶, H. Lachmann⁷, C. Lenormand⁸, V. Martinez-Taboada⁹, M. Maurer⁶, M. Peters¹⁰, R. Rizzi¹¹, F. Rongioletti¹², T. Ruzicka³, L. Schnitzler¹³, B. Schubert¹⁴, J. Sibilia¹⁵ & D. Lipsker⁸

¹Department of General Internal Medicine/Infectious Diseases, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; ²Unité d'Immuno-Hématologie, Hôpital Saint-Louis, AP-HP and Univ Paris Diderot, Paris, France; ³Department of Dermatology and Allergology, Ludwig-Maximilians University, Munich, Germany; ⁴Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; ⁵Norfolk and Norwich University Hospital, Norwich, UK; ⁶Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany; ⁷Division of Medicine, National Amyloidosis Centre, University College London Medical School, London, UK; ⁸Faculté de Médecine, Université de Strasbourg, and Clinique Dermatologique, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; ⁹Servicio de Reumatología, Hospital Universitario Marqués de Valdecilla, Santander, Spain; ¹⁰Departments of Dermatology and Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; ¹¹Department of Haematology, University of Bari Medical School, Bari; ¹²Department of Dermatology, University of Genova, Genova, Italy; ¹³3, rue GB Shaw, 75015, Paris; ¹⁴12, rue des grands champs, Brunstatt; ¹⁵Faculté de Médecine, Université de Strasbourg, and Service de Rhumatologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

To cite this article: Simon A, Asli B, Braun-Falco M, De Koning H, Fermanand J-P, Grattan C, Krause K, Lachmann H, Lenormand C, Martinez-Taboada V, Maurer M, Peters M, Rizzi R, Rongioletti F, Ruzicka T, Schnitzler L, Schubert B, Sibilia J, Lipsker D. Schnitzler's syndrome: diagnosis, treatment, and follow-up. *Allergy* 2013; DOI: 10.1111/all.12129.

Keywords

anakinra; monoclonal gammopathy; neutrophilic urticarial dermatosis; Schnitzler's syndrome; urticaria.

Correspondence

Dan Lipsker, Clinique Dermatologique, Hôpitaux Universitaires, 1, place de l'hôpital, F-67091 Strasbourg Cedex, France.
Tel.: + 33 3 88 11 61 79
Fax: + 33 3 88 11 59 62
E-mail: dan.lipsker@chru-strasbourg.fr

Accepted for publication 05 January 2013

DOI:10.1111/all.12129

Edited by: Thomas Bieber

Abstract

Schnitzler's syndrome is characterized by recurrent urticarial rash and monoclonal gammopathy, associated with clinical and biological signs of inflammation and a long-term risk of AA amyloidosis and overt lymphoproliferation. An extensive literature review was performed, and the following questions were addressed during an expert meeting: In whom should Schnitzler's syndrome be suspected? How should the diagnosis of Schnitzler's syndrome be established? How should a patient with Schnitzler's syndrome be treated? How should a patient with Schnitzler's syndrome be followed up? A diagnosis of Schnitzler's syndrome is considered definite in any patient with two obligate criteria: a recurrent urticarial rash and a monoclonal IgM gammopathy, and two of the following minor criteria: recurrent fever, objective signs of abnormal bone remodeling, elevated CRP level or leukocytosis, and a neutrophilic infiltrate on skin biopsy. It is considered probable, if only 1 minor criterion is present. In patients with monoclonal IgG gammopathies, diagnosis is definite if three minor criteria are present and possible if two are present. First-line treatment in patients with significant alteration of quality of life or persistent elevation of markers of inflammation should be anakinra. Follow-up should include clinical evaluation, CBC and CRP every 3 months and MGUS as usually recommended.

Schnitzler's syndrome was first reported in 1972 and then published as an autonomous entity in 1974 and 1989, by

Liliane Schnitzler, a French dermatologist (1–3). Its main clinical features include recurrent fever, an urticarial rash, muscle, bone, and/or joint pain, and enlarged lymph nodes. Monoclonal IgM or rarely IgG gammopathy is the biological hallmark of the disease. The physiopathological link between the features of the syndrome and the monoclonal gammopathy is still unknown, whereas interleukin-1 beta (IL-1 β) crucially contributes to the symptoms and signs of systemic inflammation, and it is unknown whether it affects the para-protein or *vice versa* (4–6). Conventional therapies including

Abbreviations

AOSD, adult-onset Still's disease; CAPS, cryopyrin-associated periodic syndrome; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HIDS, hyper-IgD syndrome; IL-1, interleukin-1; MGUS, monoclonal of undetermined significance (MGUS); SAA, serum amyloid A; SD, standard deviation; TRAPS, TNF receptor-associated periodic syndrome.

antihistamines for the skin rash, as well as anti-inflammatory drugs and immunosuppressive drugs for the systemic manifestations, are usually ineffective or too toxic. The IL-1 (interleukin 1) receptor antagonist anakinra was found to rapidly control all the symptoms of this syndrome. However, the disease recurs as soon as treatment is stopped. About 15% to 20% of patients with Schnitzler's syndrome will develop an overt lymphoproliferative disorder, as would be expected in all patients who have monoclonal IgM gammopathy of undetermined significance (MGUS) (7). The development of AA amyloidosis is a concern in untreated patients (5, 8).

Since Liliane Schnitzler's description of this syndrome, about 200 patients have been reported. To establish guidelines for the diagnosis, treatment, and follow-up of this syndrome, an expert meeting took place in Strasbourg, France, in May 2012. Although she is retired now, Liliane Schnitzler participated in the meeting and validated the conclusions. Here, we report the methodology and conclusions of this meeting.

Material and methods

A MEDLINE (National Library of Medicine, Bethesda, MD, USA) search using the key words 'Schnitzler syndrome' and 'Schnitzler's syndrome' was performed by two of the authors (DL and AS) in January 2012 to retrieve all cases. Relevant articles in English, French, and German were included. We also included cases known to us through the Schnitzler syndrome registry. This literature review was used to provide a factual basis to address the following four questions that were submitted to the experts before the meeting:

1. In whom should Schnitzler's syndrome be suspected?
2. How should the diagnosis of Schnitzler's syndrome be established?
3. How should a patient with Schnitzler's syndrome be treated?
4. How should a patient with Schnitzler's syndrome be followed up?

Only experts with recognized knowledge about Schnitzler's syndrome and who published on the topic participated in this meeting. During the first day, all issues were discussed. In the evening, two experts (DL and AS) wrote a synthesis summarizing each experts' intervention, which was submitted to second round of discussion on the second day when all points of disagreement were discussed to reach consensus, or to highlight disagreement between experts in the final paper (simplified Delphi technique).

Results

Literature review

More than 200 papers were reviewed. Cases published before 2007 were already summarized in De Koning et al.'s report of 94 patients with Schnitzler's syndrome (5). The main clinical signs of the syndrome, including an additional 102 new cases (8–43) [because of space limitations, all references cannot

Table 1 Clinical and biological findings in patients with Schnitzler's syndrome

Urticarial rash	100%
Elevated ESR (≥ 30)	95%
Fever	93%
Monoclonal IgM gammopathy	89%
Kappa light chain	89%
Arthralgia/arthritis	77%
Leucocytosis ($\geq 10\,000$)	76%
Bone pain	68%
Abnormal bone morphology*	62%
Palpable lymph nodes	47%
Pruritus	45%
Liver and/or spleen enlargement	34%

*As usually assessed by conventional X-rays.

be cited here]) since the De Koning report, thus totaling 196 patients, are shown in Table 1. Male/female ratio is 1.76, while mean and median age when first symptoms appeared were 51.6 years (SD 10 years) and 51 years, respectively. It should be highlighted that Schnitzler's syndrome is a recurrent disorder, with periods of spontaneous remission of variable duration. The rash is the most constant feature of the disorder. Detailed descriptions of this syndrome were published (4–6).

Expert consensus

In whom should diagnosis be suspected?

A chronic/recurrent urticarial rash is the hallmark feature of the disease. Together with the monoclonal gammopathy, it defines the syndrome. Patients with all signs of Schnitzler syndrome except the rash should be referred to as patients with Schnitzler-like syndrome.

Schnitzler's syndrome should be suspected in adult patients, usually older than 40 with a chronic urticarial rash associated with any of the other signs summarized in Table 2. When even one of these signs is present, appropriate tests should be performed in search of an associated monoclonal gammopathy, if not already known. Standard serum electrophoresis and immunofixation are mandatory. If negative, performing urine electrophoresis and immunofixation and serum-free light-chain measurements should be considered, as well as phenotype of blood mononuclear cells and immunoglobulin gene rearrangement study of circulating cells. Cytological, immunohistological, and molecular bone

Table 2 When should Schnitzler's syndrome be suspected?

In an adult patient with a recurrent urticarial rash and any of the following signs or symptoms
Fever
Fatigue, general malaise
Pain in joints, muscle, and/or bone
Enlarged lymph nodes, enlarged liver, or spleen
Leukocytosis and/or increased markers of inflammation
Monoclonal gammopathy
A neutrophilic infiltrate on skin biopsy

marrow studies may also be discussed in those rare cases with high clinical suspicion, no detectable monoclonal immunoglobulin, and no evidence for any differential diagnosis.

How should the diagnosis of Schnitzler's syndrome be established?

Diagnostic criteria. Since the 2001 publication of diagnostic criteria by Lipsker et al., authors have referred to those criteria in almost all subsequently published cases (4). De Koning slightly expanded the criteria by including the possibility of an IgG variant of Schnitzler's syndrome (5).

There is unfortunately no biological or other confirmative examination to allow definite diagnosis at present.

The experts felt that it is necessary to distinguish between patients with definite Schnitzler's syndrome and probable Schnitzler's syndrome, as definition of homogenous patient groups will facilitate pathogenic and therapeutic studies. Therefore, and after applying those criteria to their own series of patients, the experts agreed upon the following criteria, referred to as the Strasbourg criteria, illustrated in Table 3.

These criteria should be considered provisional until prospective validation. Their sensitivity and specificity should be established in a prospective series by comparison of patients with Schnitzler's syndrome to patients with other inflammatory diseases, including AOSD, cryoglobulinemia, chronic spontaneous urticaria, and cryopyrin-associated periodic syndrome (CAPS).

Attention should be paid to the following points:

Some diagnoses need to be excluded before application of the criteria, especially if patients are seen early in the course of the disease. They are summarized in Table 4. Some of those entities deserve a comment:

Table 3 Schnitzler's syndrome: Strasbourg diagnostic criteria

Obligate criteria	
Chronic urticarial rash +	
Monoclonal IgM or IgG	
Minor criteria	
Recurrent fever*	
Objective findings of abnormal bone remodeling with or without bone pain†	
A neutrophilic dermal infiltrate on skin biopsy‡	
Leukocytosis and/or elevated CRP§	
Definite diagnosis if	
Two obligate criteria AND at least two minor criteria if IgM, and three minor criteria if IgG	
Probable diagnosis if	
Two obligate criteria AND at least one minor criterion if IgM, and two minor criteria if IgG	

*A valid criterion if objectively measured. Must be $>38^{\circ}\text{C}$, and otherwise unexplained. Occurs usually – but not obligatory – together with the skin rash.

†As assessed by bone scintigraphy, MRI or elevation of bone alkaline phosphatase.

‡Corresponds usually to the entity described as 'neutrophilic urticarial dermatosis' (Medicine 2009;88:23–31); absence of fibrinoid necrosis and significant dermal edema.

§Neutrophils $>10\,000/\text{mm}^3$ and/or CRP $>30\text{ mg/l}$.

Table 4 Entities that should be ruled out before considering the diagnosis of Schnitzler's syndrome

For the skin lesions and/or inflammatory phenotype	
Adult-onset Still's disease	
Cryopyrin-associated periodic syndrome (especially Muckle-Wells syndrome) and other monogenic auto-inflammatory syndromes	
Urticarial vasculitis	
Cryoglobulinemic vasculitis	
Systemic lupus erythematosus	
Chronic idiopathic urticaria*	
For the monoclonal gammopathy	
Monoclonal gammopathy of unknown significance (MGUS)*	

*As both these conditions are relatively common in the elderly, these are important to consider as their co-occurrence is not exceptional.

Adult-onset Still's disease can closely mimic Schnitzler's syndrome. Both syndromes are characterized by an urticarial rash, fever, joint pain, leukocytosis, and absence of a specific diagnostic marker. Some useful features to distinguish between the two entities is the initial pharyngitis, frequent in AOSD and absent in Schnitzler's syndrome, increase in transaminases usually absent in Schnitzler's syndrome, and very elevated (low-glycosylated) ferritin levels, which are characteristic of AOSD, while ferritin rarely, if ever, exceeds 1200 ng/ml in patients with Schnitzler's syndrome (4–6).

Urticarial vasculitis, especially the hypocomplementemic variant, can also resemble Schnitzler's syndrome because of rash, fever, and joint pain. Cutaneous biopsy shows features of true vasculitis, with fibrinoid necrosis of small vessel walls, which is usually not the case in Schnitzler's syndrome. Complement consumption and anti-C1q antibodies are present, which are not observed in Schnitzler's syndrome.

Cryopyrin-associated periodic syndrome (especially Muckle-Wells syndrome or familial cold auto-inflammatory syndrome) and other auto-inflammatory disorders, such as TRAPS or mevalonate kinase deficiency syndrome [(also known as hyper-IgD syndrome (HIDS)], are usually present at a young age (especially HIDS). Development of the first symptoms after the age of 50 years would be exceptional, although some patients do not present to medical attention until late in life. A family history can help, as CAPS is inherited in an autosomal dominant fashion. A monoclonal paraprotein would not be expected.

Finally, one should not forget that both chronic idiopathic urticaria and monoclonal gammopathy (MGUS) are relatively prevalent disorders, especially in the elderly. Thus, their combination is not exceptional, and their mere association is not enough to establish the diagnosis of Schnitzler's syndrome.

How should patients with Schnitzler's syndrome be treated?

The following recommendations, summarized in Fig. 1, were agreed upon to treat patients with definite or probable Schnitzler's syndrome:

1. Patients without significant alteration in quality of life and without persistent elevation of markers of inflammation.

Exacerbating factors, if identified, should be avoided if possible. In those patients, close observation is an acceptable option. Treatment potentially targeting the inflammatory, which is probably involved in the pathogenesis of the clinical signs, seems adequate (agreement among experts). Colchicine 1–2 mg/d seems to offer a good benefit/risk ratio and was beneficial in about 25% of treated patients (4). A therapeutic trial to assess efficacy should be at least 6 months of duration. Colchicine should be ingested during a meal, because of poor digestive tolerance. Some drug interactions, especially with erythromycin and other macrolides, must be avoided.

Short-course treatments with nonsteroidal anti-inflammatory drugs, especially ibuprofen, can be used in case of time-limited exacerbations, especially of joint and bone pain (recommendation grade C).

The experts concluded that the benefit/risk ratio of thalidomide was unfavorable.

Pefloxacin was used successfully in a few patients (44, 45), but the risk of tendinopathy is significant, and the drug is not readily available in many countries. Although rarely effective, but because of low risk, a trial of hydroxychloroquine is reasonable in patients in whom joint pain is the main complaint (agreement among experts).

Experts draw attention to the fact that patients often underestimate the impact of their chronic condition on their quality of life, because of its slow onset with progression over a number of years. It is only when they are put on an effective treatment that they feel the difference.

2. Patients with significant alteration in the quality of life, and/or patients with regularly elevated inflammation markers such as ESR or CRP above the upper limit of normal.

Even in the absence of significant symptoms, this is a risk factor for the development of complications, and such patients need to be treated adequately.

Those patients should be treated with anakinra 100 mg/d subcutaneously (recommendation grade C: numerous case reports, small series, (10–43), and with strong support by

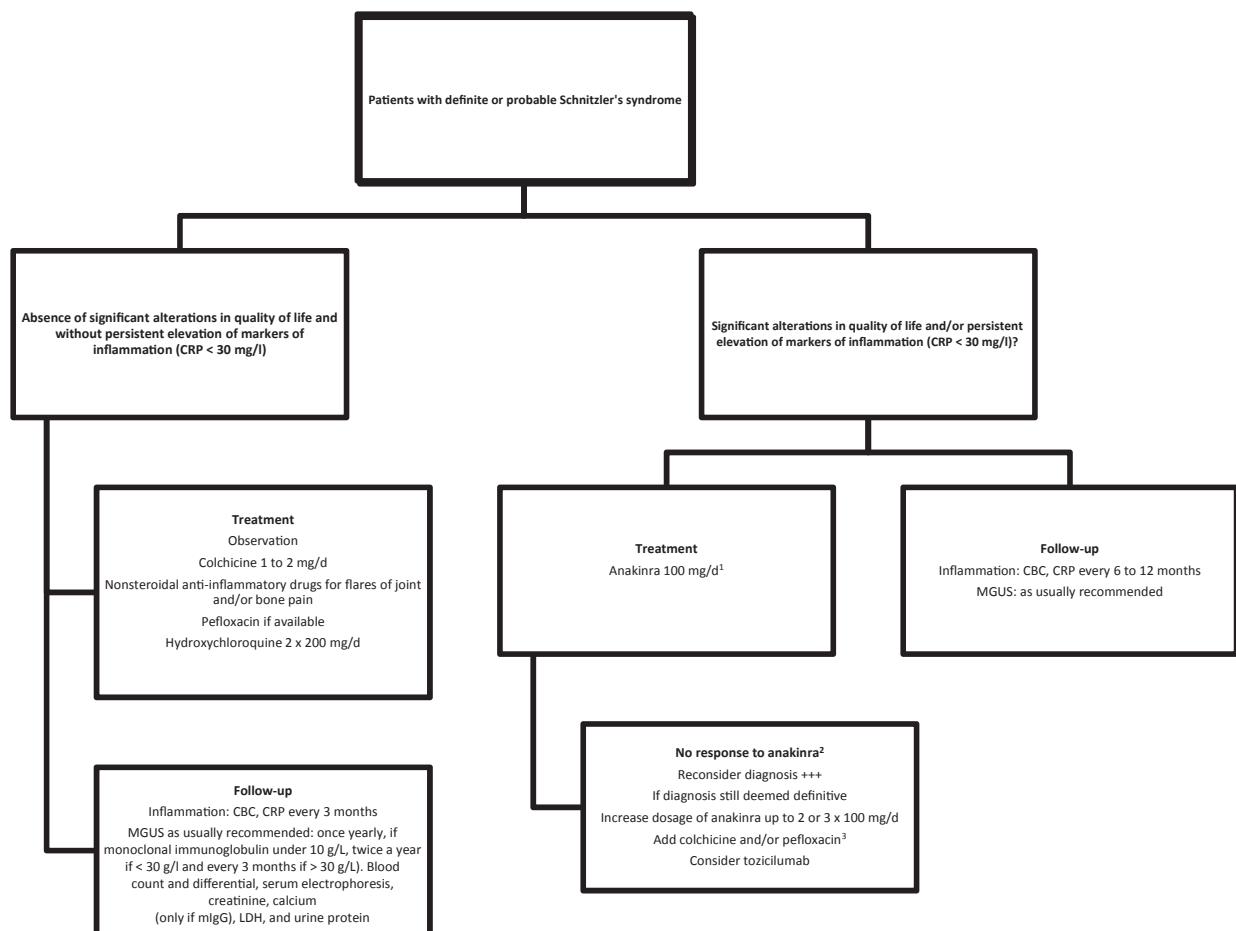


Figure 1 Treatment and follow-up recommendations for patients with definite and probable Schnitzler's syndrome. ¹As soon as patients are controlled, try to find lowest effective dosage either by

administering anakinra every other day or by lowering administered dose. ²Currently, there is very little known about this subject. ³This may be considered, although data on its efficacy are sparse.

experts). Tapering to the lowest possible dose that controls symptoms should be tried secondarily. This can be achieved either by injecting 100 mg every other day or, if signs recur on the second day, by injecting every 36 h or only part of the syringe every day (lowering the injected dose). Monitoring should include neutrophil count, liver enzymes, cholesterol, and triglycerides.

Anakinra is contraindicated in patients with hypersensitivity to the drug and when renal clearance is less than 30 ml/min. In patients with impaired renal function, the benefit/risk ratio should be evaluated and the dose of anakinra reduced if treatment deemed necessary. Pregnancy is rare in patients with Schnitzler's syndrome, as the mean age of first symptoms is more than 50 years. In case of pregnancy, treatment should be interrupted. If not possible, the benefit/risk ratio should be evaluated and discussed; very limited data suggest that anakinra does not induce malformations and can be used safely during pregnancy (46).

Because a small number of long-term remissions have been described in Schnitzler's syndrome (6, 47), it seems reasonable to propose that after a complete remission of more than 2 years' duration, treatment should be stopped to assess whether symptoms still persist. This interruption should last at least 2 weeks as flares can occur directly after anakinra is stopped (because of compensatory regulation mechanisms). Some experts (JPF, BA, DL) feel that if an interruption is considered because of complete remission, patients should first be treated with colchicine for at least 3 months and colchicine treatment should then be continued – in the absence of recurrence – for another 3–6 months.

Longer-acting IL-1 inhibitors that do not need to be injected daily seem promising alternatives (e.g. canakinumab or riloncept). However, these are more expensive, and data regarding Schnitzler's syndrome are scarce (48, 49). Furthermore, we lack data on long-term safety.

In case of failure of anakinra, diagnosis should first be reconsidered (agreement of experts). If the diagnosis is verified, anakinra dosage should be increased (up to 3×100 mg/d) and colchicine and or pefloxacin added (agreement among experts). Tocilizumab could also be considered as an alternative (50). Experts point to the fact that they do not recommend systemic steroids or nonsteroidal immunosuppressive drugs or treatments targeting MGUS (if not otherwise indicated).

How should patients with Schnitzler's syndrome be followed up?

Both the clinical and biological signs of inflammation and the monoclonal gammopathy need follow-up.

Disease activity: inflammation. Parameters of inflammation and response to treatment should be monitored by serum CRP and leukocyte count. The aim of treatment should be normalization of these values, to prevent long-term complications. These parameters should be monitored at least every 3 months. Once the patient has been established on successful treatment, parameters should be monitored at least twice a year. Serum amyloid A (SAA) protein can also be used for

monitoring, with the theoretical advantage that this combines monitoring of the acute phase response and the risk for AA amyloidosis, although the potential value of monitoring SAA in Schnitzler's syndrome has not been established.

Monoclonal gammopathy. The MGUS should be monitored as usually recommended, at a rate dependent on its serum level (once yearly if under 10 g/l, twice a year if <30 g/l, and every 3 months if >30 g/l). Blood count and differential, serum electrophoresis, creatinine, calcium (only if mIgG), LDH, and urine protein, should be measured. Changes in the characteristics of the gammopathy (such as clear increase in monoclonal Ig level) or development of lymphadenopathy should lead to consider the emergence of an overt lymphoid disorder. This should prompt to perform appropriate tests including bone marrow examination and lymph node biopsy.

Other investigations depend on comorbidities and specific treatments.

Discussion

Schnitzler's syndrome is a rare disorder with fewer than 250 known patients, although there is probably underreporting. It is considered as being a paradigm of a late-in-life-acquired auto-inflammatory syndrome. Here, we provide guidelines for diagnosis, treatment, and follow-up of patients with Schnitzler's syndrome, by using a simplified Delphi technique to reach consensus. The proposed diagnostic criteria should allow a simplified diagnosis. By separating patients in definite and probable Schnitzler's syndrome, more homogenous patient groups should be delineated. All experts agreed that IL-1 inhibition is the only regularly and completely efficient treatment for patients with Schnitzler's syndrome; patients with an alteration in their quality of life or persistent elevation of markers on inflammation should be treated with anakinra. The experts want, however, to underline the following points and unmet needs:

The here suggested Strasbourg diagnostic criteria of Schnitzler's syndrome should be evaluated prospectively, both in terms of sensitivity and specificity when applied to patients with related inflammatory disorders (AOSD, urticarial vasculitis) and in patients with chronic idiopathic urticaria.

Overall, the phenotypic characteristics of these patients should be more carefully assessed; especially, bone lesions should be more precisely investigated. We do not yet know whether they are already present in the 'early' patients (within 2 years after onset of first symptoms). The value of determining SAA as a prognostic marker should be evaluated.

Interleukin-1-neutralizing agents such as anakinra are clearly the treatment of choice in patients with Schnitzler's syndrome. These drugs should be licensed and be made available for this indication, whatever the healthcare system. Every physician taking care of patients with Schnitzler's syndrome, whatever her or his specialty, should be allowed to prescribe these drugs. A randomized controlled trial to obtain legal approval of an IL-1 inhibitor in Schnitzler's syndrome is encouraged.

Long-term efficacy of anakinra and potential secondary treatment failures must be assessed.

Delay to diagnosis is still often many years, and knowledge about this rare and sometimes debilitating syndrome should be increased.

Basic research on Schnitzler's syndrome should be encouraged, as the syndrome bears a significant impact on quality of life and probably is a paradigm of acquired diseases involving auto-inflammatory mechanisms, which are not yet understood.

To achieve some of those unmet needs, the experts encourage all clinicians who care for patients with Schnitzler's syndrome to include them in the Schnitzler syndrome database (www.schnitzlersyndrome.com). All patients with Schnitzler's-like syndrome should also be registered to increase the overall knowledge in this field.

Acknowledgments

Dan Lipsker organized the meeting. Dan Lipsker obtained a research grant from the French Dermatological Society

(Société Française de Dermatologie) to support his research on causative factors and pathomechanism involved in Schnitzler's syndrome (<http://clinicaltrialsfeeds.org/clinical-trials/show/NCT00933296>). Dan Lipsker and Anna Simon performed the literature review and wrote the initial draft of this manuscript. All authors discussed content and contributed significantly to the input of the final paper, which reflects consensus.

Conflict of interest

Anna Simon received consultancy fees from Novartis and Biovitrum; Heleen de Koning received a research support from Novartis; Victor Matinez-Taboada participated in an advisory board for SOBI laboratories; Clive Grattan attended an advisory board for SOBI laboratories; SOBI laboratories covered travel expenses and hotel accommodation for the following experts: AS, BA, HdK, JPF, CG, KK, FR, RR, and LS.

References

- Schnitzler L. Lésions urticariennes chroniques permanentes (érythème pétaïoïde ?) *Cas cliniques*, n° 46 B. Journée Dermatologique d'Angers, 28 octobre 1972.
- Schnitzler L, Schubert B, Boasson M, Gardais J, Tourmen A. Urticaire chronique, lésions osseuses, macroglobulinémie IgM: maladie de Waldenström ? 2^{ème} présentation. *Bull Soc Fr Dermatol Syphil* 1974;**81**:363.
- Schnitzler L, Hurez D, Verret JL. Urticaire chronique, ostéocondensation, macroglobulinémie. Cas princeps. Etude sur 20 ans. *Ann Dermatol Venereol* 1989;**116**:547–550.
- Lipsker D, Veran Y, Grunenberger F, Cribier B, Heid E, Grosshans E. The Schnitzler syndrome. Four new cases and review of the literature. *Medicine (Baltimore)* 2001;**80**:37–44.
- de Koning HD, Bodar EJ, van der Meer JW. Schnitzler Syndrome Study Group. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin Arthritis Rheum* 2007;**37**:137–148.
- Lipsker D. The Schnitzler syndrome. *Orphanet J Rare Dis* 2010 Dec;**8**:38.
- Kyle RA, Therneau TM, Rajkumar SV, Remstein ED, Offord JR, Larson DR et al. Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. *Blood* 2003;**102**:3759–3764.
- Claes K, Bammens B, Delforge M, Evenepoel P, Kuypers D, Vanrenterghem Y. Another devastating complication of the Schnitzler syndrome: AA amyloidosis. *Br J Dermatol* 2008;**158**:182–184.
- Kieffer C, Cribier B, Lipsker D. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases and review of the literature. *Medicine (Baltimore)* 2009;**88**:23–31.
- Martinez-Taboada VM, Fontalba A, Blanco R, Fernández-Luna JL. Successful treatment of refractory Schnitzler syndrome with anakinra: comment on the article by Hawkins et al. *Arthritis Rheum* 2005;**52**:2226–2227.
- de Koning HD, van der Meer JW, Simon A. Comment on: Schnitzler's syndrome—exacerbation after anti-TNF treatment. *Rheumatology (Oxford)* 2007;**46**:1741.
- Besada E, Nossent H. Dramatic response to IL1-RA treatment in longstanding multidrug resistant Schnitzler's syndrome: a case report and literature review. *Clin Rheumatol* 2010;**29**:567–571.
- Billey T, Beldjerd M, Popa L, Lassoued S. Schnitzler syndrome: a dramatic improvement with anakinra. *Presse Med* 2010;**39**:1338–1339.
- Cascavilla N, D'Arena G, Dell'OLio M. Schnitzler syndrome. *Br J Haematol* 2008;**143**:152.
- Cascavilla N, Bisceglia M, D'Arena G. Successful treatment of Schnitzler's syndrome with anakinra after failure of rituximab trial. *Int J Immunopathol Pharmacol* 2010;**23**:633–636.
- Crouch R, Akhras V, Sarkany R. Schnitzler's syndrome: successful treatment with anakinra. *Australas J Dermatol* 2007;**48**:178–181.
- Devlin LA, Wright G, Edgar JD. A rare cause of a common symptom Anakinra is effective in the urticaria of Schnitzler Syndrome: a case report. *Cases J* 2008;**1**:348.
- Dybowski F, Sepp N, Bergerhausen HJ, Braun J. Successful use of anakinra to treat refractory Schnitzler's syndrome. *Clin Exp Rheumatol* 2008;**26**:354–357.
- Eiling E, Möller M, Kreiselmaier I, Brasch J, Schwarz T. Schnitzler syndrome: treatment failure to rituximab but response to anakinra. *J Am Acad Dermatol* 2007;**57**:361–364.
- Eiling E, Schröder JO, Gross WL, Kreiselmaier I, Mrowietz U, Schwarz T. The Schnitzler syndrome: chronic urticaria and monoclonal gammopathy—an autoinflammatory syndrome? *J Dtsch Dermatol Ges* 2008;**6**:626–631.
- Flórez AF, Gallardo Agromayor E, García-Barredo R, Landeras Alvaro RM, Gorriño Angulo M, Martínez-Taboada VM, et al. Radiological aid to clinical diagnosis of Schnitzler's syndrome: multimodality imaging approach. *Clin Rheumatol* 2008;**27**:107–110.
- Frischmeyer-Guerrero PA, Rachamalla R, Saini SS. Remission of Schnitzler syndrome after treatment with anakinra. *Ann Allergy Asthma Immunol* 2008;**100**:617–619.
- Gilson M, Abad S, Larroche C, Dhote R. Treatment of Schnitzler syndrome with anakinra. *Clin Exp Rheumatol* 2007;**25**:931.
- Klemmer N, Lenain P, Balguerie X, Le Loët X. Effectiveness of anti-IL1 in Schnitzler's syndrome. *Joint Bone Spine* 2007;**74**:509–510.
- Kluger N, Rivière S, Guillot B, Bessis D. Efficacy of interleukin 1 receptor antagonist (anakinra) on a refractory case of

- Schnitzler's syndrome. *Acta Derm Venereol* 2008;**88**:287–288.
26. Larocca CA, McEvoy JW, Ellis CL, Junkins-Hopkins J, Kolb T, Baer AN et al. Schnitzler's syndrome associated with pancreatitis: a disease of IL-1 dysregulation. *Clin Rheumatol* 2012;**31**:169–174.
 27. Lee KY, Grattan CE. Intracostal neuralgia as a previously undescribed symptom of Schnitzler's syndrome. *Br J Dermatol* 2012;**167**:1392–1393.
 28. Loock J, Lamprecht P, Timmann C, Mrowietz U, Csernok E, Gross WL. Genetic predisposition (NLRP3 V198M mutation) for IL-1-mediated inflammation in a patient with Schnitzler syndrome. *J Allergy Clin Immunol* 2010;**125**:500–502.
 29. Ryan JG, de Koning HD, Beck LA, Booty MG, Kastner DL, Simon A. IL-1 blockade in Schnitzler syndrome: ex vivo findings correlate with clinical remission. *J Allergy Clin Immunol* 2008;**121**:260–262.
 30. Saiz E, Gálvez J, Mora A, Contreras L. Anakinra and Schnitzler's syndrome. *Med Clin (Barc)* 2008;**130**:358–359.
 31. Schneider SW, Gaubitz M, Luger TA, Bonsmann G. Prompt response of refractory Schnitzler syndrome to treatment with anakinra. *J Am Acad Dermatol* 2007;**56**(5 Suppl):S120–S122.
 32. Schuster C, Kränke B, Aberer E, Arbab E, Sturm G, Aberer W. Schnitzler syndrome: response to anakinra in two cases and review of the literature. *Int J Dermatol* 2009;**48**:1190–1194.
 33. Sokumbi O, Drage LA, Peters MS. Clinical and histopathologic review of Schnitzler syndrome: the Mayo Clinic experience (1972–2011). *J Am Acad Dermatol* 2012;**67**:1289–1295.
 34. Szturz P, Adam Z, Hájek R, Mayer J. Successful anakinra therapy in 2 patients with Schnitzler syndrome. *Onkologie* 2011;**34**:265–268.
 35. Szturz P, Adam Z, Sedivá A, Fojtík Z, Corbová D, Neubauer J et al. Schnitzler syndrome: diagnostics and treatment. *Klin Onkol* 2011;**24**:271–277.
 36. Terpos E, Asli B, Chistoulas D, Brouet JC, Kastiris E, Rybojad M et al. Increased Angiogenesis and Enhanced Bone Formation in Patients with IgM Monoclonal Gammopathy and Urticarial Skin Rash: New Insight into the Biology of the Schnitzler Syndrome. *Haematologica* 2012;**97**:1699–1703.
 37. Thonhofer R, Uitz E, Graninger W. Schnitzler's syndrome–exacerbation after anti-TNF treatment. *Rheumatology (Oxford)* 2007;**96**:1041–1042.
 38. Tinazzi E, Puccetti A, Patuzzo G, Sorleto M, Barbieri A, Lunardi C. Schnitzler syndrome, an autoimmune-autoinflammatory syndrome: report of two new cases and review of the literature. *Autoimmun Rev* 2011;**10**:404–409.
 39. Treudler R, Kauer F, Simon JC. Striking effect of the IL-1 receptor antagonist Anakinra in chronic urticarial rash with polyclonal increase in IgA and IgG. *Acta Derm Venereol (Stockh)* 2007;**87**:280–281.
 40. van Deuren M, Kroot JJ, Swinkels DW. Time-course analysis of serum hepcidin, iron and cytokines in a C282Y homozygous patient with Schnitzler's syndrome treated with IL-1 receptor antagonist. *Haematologica* 2009;**94**:1297–1300.
 41. Vandenhende MA, Bentaberry F, Morlat P, Bonnet F. Anakinra: an effective treatment in the Schnitzler syndrome. *Joint Bone Spine* 2011;**78**:636–637.
 42. Volz T, Wölbing F, Fischer J, Braun M, Maggosschitz I, Schaller M et al. Dermal Interleukin-1 Expression and Effective and Long-lasting Therapy with Interleukin-1 Receptor Antagonist Anakinra in Schnitzler Syndrome. *Acta Derm Venereol* 2012;**92**:393–394.
 43. Wastiaux H, Barbarot S, Gagey-Caron V, Berthelot JM, Hamidou M, Stalder JF. Schnitzler syndrome: a dramatic improvement with anakinra. *J Eur Acad Dermatol Venereol* 2009;**23**:85–87.
 44. Asli B, Bienvenu B, Cordoliani F, Brouet JC, Uzunhan Y, Arnulf B et al. Chronic urticaria and monoclonal IgM gammopathy (Schnitzler syndrome): report of 11 cases treated with pefloxacin. *Arch Dermatol* 2007;**143**:1046–1050.
 45. Kastiris E, Katoulis A, Terpos E, Panayiotides I, Gavriatopoulou M, Dimopoulos MA. Schnitzler's syndrome: increased levels of bone formation and angiogenesis factors are reduced after successful pefloxacin treatment. *Clin Lymphoma Myeloma* 2008;**8**:359–362.
 46. Fischer-Betz R, Specker C, Schneider M. Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra). *Clin Exp Rheumatol* 2011;**29**:1021–1023.
 47. Asli B, Brouet JC, Ferman JP. Spontaneous remission of Schnitzler syndrome. *Ann Allergy Asthma Immunol* 2011;**107**:87–88.
 48. de Koning HD, Schalkwijk J, van der Meer JW, Simon A. Successful canakinumab treatment identifies IL-1 β as a pivotal mediator in Schnitzler syndrome. *J Allergy Clin Immunol* 2011;**128**:1352–1354.
 49. Krause K, Weller K, Stefaniak R, Wittkowski H, Altrichter S, Siebenhaar F et al. Efficacy and safety of the interleukin-1 antagonist rilonacept in Schnitzler syndrome: an open-label study. *Allergy* 2012;**67**:943–950.
 50. Krause K, Feist E, Fiene M, Kallinich T, Maurer M. Complete remission in 3 of 3 anti-IL-6-treated patients with Schnitzler syndrome. *J Allergy Clin Immunol* 2012;**129**:848–850.