Retention rate of IL-1 inhibitors in Schnitzler's syndrome

F. Crisafulli[1], A. Vitale[2], P. Airò[1], M. Grigis[1], C. Gaggiano[2], L. Dagna[3], G. Cavalli[3], R. Cimaz[4], O. Viapiana[5], F. Iannone[6], G. Lopalco[6], R. Bortolotti[7], M. Abdel Jaber[7], C. Montecucco[8], S. Monti[8], S. Balduzzi[8], G. Emmi[9], I. Mattioli[9], F. Franceschini[1], L. Cantarini[2], M. Frassi[1]

[1]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili and University of Brescia, Italy; [2]Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy; [3]Vita-Salute San Raffaele University, Milan, Italy; Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UniRAR), IRCCS San Raffaele Scientific Institute, Milan, Italy; [4]Department of Clinical Sciences and Community Health, Research Center for Adult and Paediatric Rheumatic Diseases, Università degli Studi di Milano, Milan, Italy; Division of Paediatric Rheumatology, ASST Gaetano Pini-CTO Institute, Milan, Italy; [5]Rheumatology Unit, University of Verona, Policlinico G.B. Rossi, Verona, Italy; [6]Rheumatology Unit, Department of Emergency and Organ Transplantations, University of Bari Aldo Moro, Bari, Italy; [7]Department of Rheumatology, Santa Chiara Hospital, Trento, Italy; [8]Department of Rheumatology, IRCCS Fondazione Policlinico S. Matteo, Pavia; University of Pavia, Italy; [9]Department of Experimental and Clinical Medicine, University of Florence; Italy.

Abstract

Objective

Schnitzler's syndrome is a rare autoinflammatory disease. Clinical response to IL-1 inhibitor drugs has been described, but limited information is available on the long-term efficacy and safety of these agents in Schnitzler's syndrome.

Methods

A retrospective study was conducted of patients with Schnitzler's syndrome fulfilling Strasbourg diagnostic criteria followed in 9 Italian centres. The retention rate of IL-1 inhibitors was evaluated using Kaplan-Meier analysis.

Results

Fifteen of 20 patients with Schnitzler's syndrome were treated with IL-1 inhibitors: in total, they received 16 courses of anakinra (median duration 20.0 months [6.0–58.3]), and 8 courses of canakinumab (median duration 19.0 months [13.5–31.0]). The retention rate of IL-1 inhibitors was 73.4% [SE 9.4] at 1 year and 63.6% [SE 10.4] at 2 years. There was no significant difference between the retention rate of anakinra and canakinumab. The retention rate was higher in patients with a definite diagnosis according to the Strasbourg criteria as compared with those with a probable diagnosis (p=0.03). At the last follow-up visit, all patients who started therapy with IL-1 inhibitors were still on treatment, although in some cases with an increased dosage compared to the start of therapy. A sparing effect on the use of conventional synthetic disease-modifying anti-rheumatic drugs and a significant reduction of prednisone dosage (p=0.02) and of serum amyloid A (SAA) levels (p=0.03) were observed.

Conclusion

The retention rate of IL-1 inhibitors in patients with Schnitzler's syndrome was high, particularly in patients with a definite diagnosis according to the Strasbourg criteria, reflecting their effectiveness in the treatment of this syndrome.

Key words

Schnitzler's syndrome, anakinra, canakinumab, urticaria, monoclonal gammopathy, fever

Francesca Crisafulli, MD
Antonio Vitale, MD
Paolo Airò, MD
Marco Grigis, MD
Carla Gaggiano, MD
Lorenzo Dagna, MD, Prof.
Giulio Cavalli, MD, PhD
Rolando Cimaz, MD, Prof.
Ombretta Viapiana, MD, Prof.
Florenzo Iannone, MD, Prof.
Giuseppe Lopalco, MD, Prof.
Roberto Bortolotti, MD
Masen Abdel Jaber, MD
Carlomaurizio Montecucco, MD, Prof.
Sara Monti, MD
Silvia Balduzzi, MD
Giacomo Emmi, MD, Prof.
Irene Mattioli, MD
Franco Franceschini, MD, Prof.
Luca Cantarini, MD, Prof.
Micol Frassi, MD

Please address correspondence to:
Francesca Crisafulli,
ASST Spedali Civili di Brescia,
U.O. di Reumatologia
e Immunologia Clinica,
Piazzale Spedali Civili 1,
25123, Brescia, Italy.
E-mail: crisafulli.francesca10@gmail.com

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Introduction

Schnitzler's syndrome is a rare autoinflammatory disease, described for the first time in 1970, and characterised by the presence of a serum monoclonal gammopathy (most frequently IgM-type) with recurrent episodes of hives, accompanied by clinical and laboratory signs of acute inflammation (1-5). The clinical phenotype is variable and the associated signs and symptoms may include recurrent fever, weight loss, bone and articular pain, lymphadenopathy, hepatosplenomegaly and neuropathy (3, 5). Although in 2012 diagnostic criteria were set out allowing a definite or probable diagnosis to be made (1), Schnitzler's syndrome remains an underdiagnosed disease with the consequent delay of the initiation of specific treatment (6). The most serious complications observed in patients with Schnitzler's syndrome are the development of lymphoproliferative disease in 15–20% of cases, and, more rarely, in untreated patients, of amyloid A (AA) amyloidosis (2, 3, 5).

Although the exact pathogenic mechanisms of Schnitzler's syndrome have not yet been fully clarified, many clinical and laboratory features allow us to frame it in an acquired autoinflammatory disease (7, 8). In fact, similar to cryopyrin-associated periodic syndromes, its pathophysiology seems to indicate an exaggerated activation of the inflammasome, an intracellular multiprotein complex synthetising IL-1 in response to cell stress (9). Accordingly, high levels of IL-6 and IL-18 have been demonstrated in serum of patients with Schnitzler's syndrome (10, 11). Moreover, in mastocytes of both damaged and healthy skin of patients with Schnitzler's syndrome, an hyperproduction of IL-1β was detected (12), and clinical response to IL-1 inhibitor drugs was observed (8, 11). Nevertheless, the link between the monoclonal gammopathy and the mechanisms leading to lymphoproliferative disease remains to be clarified (7, 8).

Different studies have described the effectiveness of IL-1 inhibitors in Schnitzler's syndrome (1, 3, 14-23), but so far there is limited information available on the long-term efficacy and safety of these agents. Moreover, the optimal dosage of these drugs is still unknown. For these reasons, we retrospectively evaluated an Italian multicentre cohort of patients with Schnitzler's syndrome, focusing particularly on these issues.

Patients and methods

Study design and patient population

We conducted a multicentre non-interventional retrospective study that was approved by the Ethics Committee of Azienda Ospedaliera Universitaria Senese, Siena, Italy (AIDA Project; ref. no. 14951).

Data from all patients with a clinical diagnosis of Schnitzler's syndrome were collected anonymously from 9 Italian centres, participating in the study group of autoinflammatory diseases of the Italian Society for Rheumatology (SIR). Inclusion criteria of patients were: age ≥18 years; definite or probable diagnosis of Schnitzler's syndrome, according to the Strasbourg diagnostic criteria (1). Two patients who did not fulfill the Strasbourg criteria were therefore excluded from the analysis.

The data were entered into a standardised database which included the following information: demographic data, Strasbourg major (chronic urticarial rash + monoclonal IgM or IgG) and minor (recurrent fever, objective findings of abnormal bone remodelling with or without bone pain, a neutrophilic dermal infiltrate on skin biopsy; leukocytosis and/or elevated C Reactive Protein (CRP)) criteria, data of disease onset and diagnosis, other relevant clinical features (arthritis/arthralgia, weight loss, angioedema, lymphadenopathy, splenomegaly, hepatomegaly, neuropathy), laboratory data (erythrocyte sedimentation rate (ESR), CRP, anaemia, monoclonal gammopathy, Bence Jones protein), genetic analysis, skin biopsy, development of haematological malignancies, and treatment. Clinical and laboratory data, as well as medications at the last available visit, were also recorded. Complete remission was defined as the absence of fever, urticarial rash/angioedema and arthralgia/arthritis, with normal ESR and CRP.

Statistical analysis

Categorical variables were expressed as number (%) and were compared using

Fisher exact test. Continuous variables were expressed as median [25th–75th percentile] and were compared using Mann-Whitney test or Wilcoxon sign-rank test for paired measurements. The retention rate of IL-1 inhibitors was evaluated using Kaplan-Meier Analysis; the log-rank test was used to compare retention rates of different groups.

Results

Twenty patients (10 females, 10 males) diagnosed with Schnitzler's syndrome from January 2001 to December 2019 were included. Their main clinical and laboratory features are described in Table I. According to the Strasbourg diagnostic criteria, 13 (65%) patients had a definite diagnosis and 7 (35%) had a probable diagnosis. The median age at the time of the diagnosis was 58.0 years, whereas at the onset of symptoms it was 55.5 years. The median diagnostic delay was 2 years (1-4).

Clinical and laboratory features

All patients presented with a chronic urticarial rash. The second most common clinical manifestation was intermittent fever (more than 38°C) in 19 patients (95%). Sixteen patients (80%) had arthralgia or arthritis, and 14 patients (70%) had pruritus. Other clinical features were observed in a minority of patients.

Twelve patients (60%) had IgM paraprotein and 6 patients (30%) had IgG paraprotein; 2 patients (10%) had a double monoclonal gammopathy (Table I). Bence Jones protein was found in 6 out of 20 patients (30%). All patients had raised inflammatory indexes; leukocytosis was present in 14 patients (70%) and anaemia in 7 (35%).

Genetic analyses for known autoinflammatory diseases were performed in 7 patients (35%), all of which tested negative.

Treatments

All patients received corticosteroids with a median higher dose of 25 mg/d [25–30]; in 1 case (5%), this was the only treatment, as a good clinical response was observed.

Four patients (20%) were treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) as the only non-steroidal agents, whereas 15 patients received one or more biological disease-modifying anti-rheumatic drugs (bDMARDs), in 11 cases (73%) after failure of one or more cs-DMARDs.

Table I. Demographic, clinical and laboratory features of the total cohort and of patients treated without or with bDMARDs.

	Total (20)	No bDMARDs (5)	bDMARDs (15)	*p*
Demographic characteristics				
Age at diagnosis, median [IQR] years	58.0 [54.5-66.5]	55.0 [49.0-55.0]	64.0 [56.0-72.5]	0.06
Age at disease onset, median [IQR] years	55.5 [51.3-62.3]	53.0 [46.0-54.0]	61.0 [52.5-67.5]	0.11
Disease duration prior to diagnosis, median [IQR] years	2.0 [1.0-4.0]	2.0 [1.0-4.0]	2.0 [1.0-4.0]	0.97
Sex, M/F	10/10	3/2	7/8	1.0
Clinical features				
Chronic urticarial rash, n (%)	20 (100%)	5 (100%)	15 (100%)	1.0
Pruritus, n (%)	14 (70%)	5 (100%)	9 (60%)	0.26
Intermittent fever, n (%)	19 (95%)	5 (100%)	14 (93%)	1.0
Arthralgia/Arthritis, n (%)	16 (80%)	5 (100%)	11 (73%)	0.53
Bone pain, n (%)	8 (40%)	2 (40%)	6 (40%)	1.0
Weight loss, n (%)	9 (45%)	2 (40%)	7 (47%)	1.0
Angioedema, n (%)	3 (15%)	1 (20%)	2 (13%)	1.0
Lymphoadenopathy, n (%)	7 (35%)	2 (40%)	5 (33%)	1.0
Hepatomegaly, n (%)	2 (10%)	0	2 (13%)	1.0
Splenomegaly, n (%)	2 (10%)	0	2 (13%)	1.0
Neuropathy, n (%)	3 (15%)	0	3 (20%)	0.53
Laboratory features				
Raised ESR or CRP, n (%)	20 (100%)	5 (100%)	15 (100%)	1.0
Leukocytosis, n (%)	14 (70%)	4 (80%)	10 (67%)	1.0
Anaemia, n (%)	7 (35%)	1 (20%)	6 (40%)	0.61
Monoclonal gammopathy, n (%)	20 (100%)	5 (100%)	15 (100%)	1.0
IgM total	13 (65%)	4 (80%)	9 (60%)	0.61
IgM κ	12 (60%)	4 (80%)	8 (53%)	0.60
IgM λ	1 (5%)	0	1 (7%)	1.0
IgG total	9 (45%)	2 (40%)	7 (47%)	1.0
IgG κ	5 (25%)	0	5 (33%)	0.27
IgG λ	4 (20%)	2 (40%)	2 (13%)	0.25
IgGλ and IgG κ	1 (5%)	0	1 (7%)	1.0
IgM κ and IgGλ	1 (5%)	1 (20%)	0	0.25
Bence Jones protein	5 (25%)	1 (20%)	4 (27%)	1.0

The demographic, clinical and laboratory features of patients treated with or without bDMARDs ('bDMARDs' *versus* 'no bDMARDs' groups) are listed in Table I. No significant differences were observed between these two groups. Thus, no predictor of bDMARDs need could be identified.

Among patients treated only with csDMARDs, 3 (75%) were initially treated with colchicine (median dosage 1.5 mg/d [1.25–1.5]), which was effective in all cases in symptoms control (in 1 patient it was stopped after 5 years for remission). One patient was initially treated with sulfasalazine 2 g/d, that was withdrawn for primary inefficacy; the introduction of cyclosporine at the dosage of 200 mg/d was effective in disease control.

In 15 patients, bDMARD treatment was started, after a median time of 30 months from diagnosis [9-78]. Previous treatments with csDMARDs in 11 cases included methotrexate (n=5), colchicine (n=5), cyclosporine (n=3), azathioprine (n=1), mycophenolate mofetil (n=1), cyclophosphamide (n=1).

In 14 patients, anakinra was the first line biologic choice at the standard dosage of 100 mg/d (200 mg/d during exacerbations in 1 case), whereas tocilizumab was the first choice in 1 patient. In 7 (50%) patients anakinra was continued with benefit for the whole follow-up period. In the other 7 patients, the treatment was discontinued: in 3 cases because of secondary inefficacy, after a median time of 18 months [15-40]; in 3 cases due to adverse events, consisting in 2 injection site reactions, after 1.5 months [1.25–1.75], and 1 se-

vere generalised skin rash; in 1 case due to both secondary inefficacy and leukopenia, after 43 months from the start of anakinra.

After discontinuation of anakinra, 5 patients were treated with canakinumab as second line biologic treatment (150 mg/8weeks in 4 cases and 150 mg/4weeks in 1), resulting in a complete response in 2 cases (after dose adjustment from 150 mg/8weeks to 150 mg/4weeks in one patient, and from 150 mg/4weeks to 300 mg/4weeks in another case), partial response in 2 cases (at the dosage of 150 mg/8weeks and 150 mg/4weeks) and no response in 1 case (at the dosage of 150 mg/4weeks). No response was observed in 3 patients treated with TNF inhibitors as a second or third line bDMARDs, as well as in the case initially treated with tocilizumab: in all these patients a good response was afterwards obtained with canakinumab (3 cases; 1 patient resumed canakinumab after a brief trial with etanercept for persistent arthritis) or anakinra (1 case was treated at the dosage of 200 mg/d after having shown only partial efficacy with the standard dosage of 100 mg/d, and an unsuccessful attempt with infliximab).

In summary, 15 patients received a total of 24 courses of IL-1 inhibitor treatment (16 with anakinra and 8 with canakinumab), with a median course duration of 19 months [8.5–51.3]. Fifteen patients received anakinra (14 as first line treatment, 1 as second line after tocilizumab failure), and the treatment was confirmed in 8 of them. The median duration of the courses of anakinra was 20.0 months [6.0–58.3].

Six of the 7 patients who received canakinumab continued the treatment: 4 as second line treatment after anakinra failure, 2 as third line treatment (1 after tocilizumab and anakinra failures and 1 after anakinra and adalimumab failures); in 1 patient it was resumed after an attempt with etanercept that was the third line treatment after anakinra and canakinumab. The median duration of the courses of canakinumab was 19.0 months [13.5–21.0].

The retention rate of IL-1 inhibitor courses was 73.4% [SE 9.4] at 1 year and 63.6% [SE 10.4] at 2 years. There

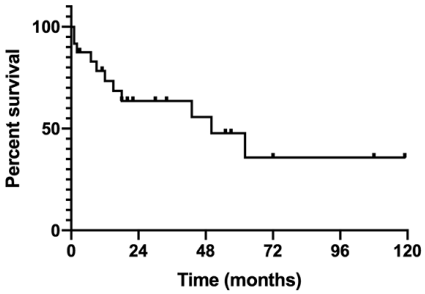

Fig. 1. Retention rate of IL-1 inhibitors (24 courses).

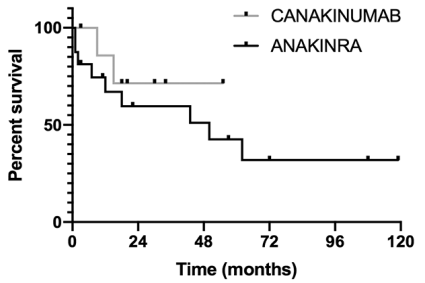

Fig. 2. Retention rate of canakinumab and anakinra (8 and 16 courses, respectively). Log rank test: p=0.41.

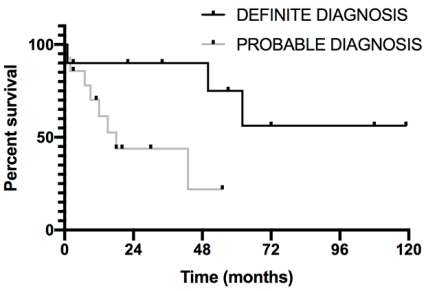

Fig. 3. Retention rate of IL-1 inhibitors in patients with definite (n=8) or probable (n=7) diagnosis, according to Strasbourg criteria. Log rank test: p=0.03.

was no significant difference between the retention rates of courses with anakinra (at 1 year: 67.0% [12.2]; at 2 years: 59.6% [12.9]) or canakinumab (at 1 year: 85.7% [13.2]; at 2 years 71.4% [17.1]) (log-rank test: p=0.41) (Fig. 1-2). The retention rate of IL-1 inhibitors was higher in patients with definite diagnosis of Schnitzler's syndrome according to the Strasbourg criteria (at 1 year: 90.0% [9.5]; at 2 years: 90.0% [9.5]) compared with those with probable diagnosis (at 1 year: 61.4% [13.7]; at 2 years: 43.8% [14.4]) (log-rank test: p=0.03) (Fig. 3).

Last follow-up visit

The median follow-up from diagnosis was 5.5 years [2.0–9.0]. The median

Table II. Clinical-laboratory features and IL-1 inhibitor dosage of 13 patients treated with bDMARDs at last follow-up visit.

Clinical features	
Chronic urticarial rash, n (%)	0
Pruritus, n (%)	1 (8%)
Intermittent fever, n (%)	0
Arthralgia/Arthritis, n (%)	3 (23%)
Bone pain, n (%)	0
Weight loss, n (%)	0
Angioedema, n (%)	1 (8%)
Lymphoadenopathy, n (%)	0
Hepatomegaly, n (%)	1 (8%)
Splenomegaly, n (%)	0
Neuropathy, n (%)	1 (8%)
Laboratory features	
Raised ESR or CRP, n (%)	1 (8%)
Leukocytosis, n (%)	0
Anaemia, n (%)	1 (8%)
IL-1 inhibitor dosage	
Anakinra, n (%)	7 (54%)
100 mg/die, n (%)	6 (46%)
200 mg/die, n (%)	1 (8%)
Canakinumab n (%)	6 (46%)
150 mg/8 weeks, n (%)	2 (15%)
150 mg/4 weeks, n (%)	3 (23%)
300 mg/4 weeks, n (%)	1 (8%)

duration of the last bDMARD treatment was 30.0 months [16.5–56.0]; in particular, the median duration of anakinra was 53.5 months [19.3–81.0] and of canakinumab was 20 months [16.5–32.0].

During follow-up myelodysplastic syndrome was diagnosed in 2 patients (1 year after disease onset in both cases). In 1 case monoclonal gammopathy evolved into multiple myeloma, and the patient died 15 years after the onset of symptoms (while on treatment with anakinra) for multiple myeloma complications. Another patient, with concomitant peripheral artery disease, died during follow-up. He interrupted canakinumab treatment (150 mg/8weeks) when admitted for lower limb arterial revascularisation surgery, which was followed by a forefoot amputation. He died 3 months after the last canakinumab dose while following a rehabilitation programme.

Clinical and laboratory features and IL-1 inhibitor dosage of patients treated with bDMARDs at the last follow-up visit are reported in Table II.

Paired data of serum paraprotein level were available in 5 patients treated with bDMARDs: no difference was observed between baseline levels prior to the last IL-1 inhibitor (0.45 g/dL

[0.22–0.50]), and last follow-up visit (0.22 g/dL [0.20–0.70]; *p*=0.6*)*. Paired data of serum amyloid A (SAA) levels were available in 6 patients: a significant decrease from baseline, before the start of the last IL-1 inhibitor, to the last follow-up visit was observed (from 226.7 mg/L [150.3–276.5] to 7.3 mg/L [4.2–127.3]; *p*=0.03).

As regards medication, 2 patients (11%) were off treatment, 3 patients (17%) were on treatment with csDMARDs without concomitant bDMARDs, and 13 patients (72%) were on treatment with a bDMARD (IL-1 inhibitor in all cases). In detais, 1 patient was treated with colchicine; 1 patient with colchicine plus prednisone 2.5 mg/d; 1 patient with cyclosporine 100 mg/d plus prednisone 5 mg/d; 7 patients (39%) with anakinra (6 at the dosage of 100 mg/d, 1 at the dosage of 200 mg/d) and 6 patients (33%) with canakinumab (2 at the dosage of 150 mg/8 weeks, 3 at the dosage of 150 mg/4 weeks and 1 at the dosage of 300 mg/4 weeks). Notably, in 2 patients the initial dosage of canakinumab was increased during follow-up. Six out of 7 patients (86%) on treatment with anakinra were in complete remission, whereas 1 patient had arthralgia/arthritis. Two out of 6 patients (33%) on treatment with canakinumab, were in complete remission while 4 had some residual active manifestations.

Overall, three patients who were on treatment with prednisone at the start of the last IL-1 inhibitor discontinued it. Although treatment with IL-1 inhibitors was still associated with corticosteroids in 7 patients, the prednisone median dose significantly decreased from 12.5 mg/d [10.0–18.8] to 5 mg/d [0–7.5] (*p*=0.02) at the last follow-up visit. Moreover, since treatment with IL-1 inhibitors at the last follow-up visits was associated with csDMARD use only in 2 patients (methotrexate 20 mg/week and methotrexate 10 mg/week + cyclosporine 100 mg/d, respectively), a relevant csDMARDs sparing effect was observed.

Discussion

To our knowledge, this is the first study evaluating the effectiveness of IL-1 inhibitor treatment in Schnitzler's syndrome by assessing their retention rate. In this multicentre cohort, treatment with IL-1 inhibitors as first, second or third line bDMARD obtained good disease control as well as corticosteroid reduction in patients who did not respond to csDMARDs and/or to other prior bDMARDs. Interestingly, we observed a better retention rate in patients with a definite diagnosis of Schnitzler's syndrome according to the Strasbourg criteria, as compared with those with a probable diagnosis suggesting possible better effectiveness of these agents in patients with full-blown spectrum of the syndrome. Our data are in agreement with different studies in which the efficacy of IL-1 inhibitors was observed (3, 14-16, 18-21).

Néel *et al*. reported that among 29 patients treated with anakinra, 83% were in complete remission at 36 months, whilst 17% were in partial remission, and no one stopped the drug due to adverse reactions; 5 patients (17%) suffered from injection site reaction without suspending the treatment (14). More recently, Rowczenio *et al*. pointed out that 95% of 20 patients with Schnitzler's syndrome reported the disappearance of all symptoms during anakinra treatment (10). These figures might appear even higher than those observed in our cohort, although it should be noted that slight differences in the definition of complete remission were used, and that the proportion of patients with definite or probable diagnosis according to the Strasbourg criteria was not reported in previous studies (10,14). Moreover, details of anakinra dosage were not described in all patients (10, 14). Nevertheless, in our cohort, at the last available follow-up visit, 86% of patients on treatment with anakinra were in complete remission and only 1 patient complained of arthralgias.

Canakinumab was also reported to be effective in disease control (18-21), although there is no consensus on the dosage: in a placebo-controlled study the rate of complete clinical response was significantly higher in the canakinumab-treated patients than in the placebo group (5 of 7 *vs*. 0 of 13 patients) (18). In the open-label follow-up phase of this trial, the duration of clinical improvement after canakinumab administration showed major interindividual differences, and retreatments were necessary with variable drug doses and intervals (18). Nevertheless, the long-term efficacy of this flexible approach was demonstrated by a 4-year extension study of this trial (19). In another open-label trial, canakinumab was administered to 8 patients with Schnitzler's syndrome at the dose of 150 mg/4 weeks for 6 months and was effective in 7 patients, while 1 patient had a relapse during treatment and returned to anakinra (20).

In our multicentre cohort, at the start of treatment, the most frequently used scheme of canakinumab was 150 mg/8 weeks, but at the last follow-up visit only 1 patient was in complete remission at this dosage. Four out of the 6 remaining patients still suffered from some disease manifestations despite the increase to 150 mg/4 weeks in one case, while a further patient required canakinumab 300 mg/4 weeks to reach complete disease control. The optimal dosage of canakinumab in patients with Schnitzler's syndrome remains to be determined and the dosage should probably be established for each individual patient. This is also true for anakinra: in fact, in 1 case a complete response was obtained with the increase of the dosage to 200 mg/d. In this variegated scenario, an increase of the dosage of the IL-1 inhibitor should be considered in order to tailor the treatment to the single patient. Future studies are needed to evaluate possible predictive factors of high dosage IL-1 inhibitor requirement.

Our data confirmed previous studies that reported the safety of IL-1 inhibitors (21): in our cohort, anakinra was withdrawn in 4 out of 15 patients: due to generalised skin rash in 1 patient, injection site reactions in 2 cases and leukopenia in 1 patient. Although these data are reassuring, it should be noted that recently, a case of anakinra-induced psoriasis in a patient with Schnitzler's syndrome was described (24).

The retention rate of IL-1 inhibitor cycles of therapy was 73.4% at 1 year and 63.6% at 2 years, with no significant

difference between anakinra and canakinumab. These data are a further demonstration of the effectiveness of IL-1 inhibitors in the treatment of Schnitzler's syndrome and of the persistence of a good clinical response.

Since both agents were effective, the therapeutic choice between them should be made for each individual patient, considering the mode and frequency of administration, the half-life of the drug and the possibility of making dosage changes. The choice should therefore consider the compliance of the patient, but also the manageability of the drug in the case of side effects, as well as the costs of drugs.

As described by others (19-21, 25), we have observed a significant reduction in SAA levels in patients treated with IL-1 inhibitors. This is further evidence of efficacy and might suggest a role of these agents in preventing the onset of AA amyloidosis, a rare, but serious, long-term complication in patients with Schnitzler's syndrome (3).

It is known that these patients may develop lymphoproliferative malignancies, mainly Waldenström macroglobulinaemia in about 15% of cases (25). As previously reported by others (16, 19, 20, 25), the monoclonal gammopathy remained stable during the follow-up period in the present study, and only 1 case of evolution to multiple myeloma was observed, in a patient with long-standing disease. Although no apparent effect of IL-1 inhibitor treatment on the serum paraprotein level was observed, our observation did not disclose possible adverse effects of these agents on the progression to lymphoproliferative diseases.

Interestingly, we observed myelodysplastic syndromes in 2 patients. Although, to our knowledge, this association was never previously reported, it is well known that patients with monoclonal gammopathy of undetermined significance, or with multiple myeloma, have an increased risk of developing myelodysplastic syndromes (26, 27). This highlights the need to monitor patients with Schnitzler's syndrome also for this complication. Moreover, the recently described adult-onset, X-linked, severe autoinflammatory disease caused by somatic mutations in UBA1, also known as VEXAS syndrome (28), should be considered in the differential diagnosis of Schnitzler's syndrome, particularly when myelodysplasia is also present.

Our study suffers from many limitations, including the limited number of patients, the retrospective design, and the number of missing data on longitudinal SAA values and monoclonal gammopathy evaluation. Nevertheless, our observations confirm the long-term safety of IL-1 inhibitors and their efficacy in controlling clinical manifestations and reducing inflammation in patients with Schnitzler's syndrome. This may not only prevent the onset of disease relapse and long-term complications, such as AA amyloidosis, but also allows a substantial sparing effect on corticosteroid use. Treatment with IL-1 inhibitors has been advised by other authors in patients with significant alterations in quality of life and/or persistent CRP elevation (1). We suggest that the need for long-term moderate-to-high dose of glucocorticoids might be a further indication for the use of these agents in Schnitzler's syndrome.

Our experience suggests that the optimal dosage of these agents needs to be tailored to every patient and that a dose increase should be considered before discontinuing IL-1 inhibitor treatment, in the case of inefficacy. Prospective studies are needed to better define these issues.

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