IL-1 targeting agents in Schnitzler syndrome: a multicentre, real-world study from the international AIDA Network Schnitzler Registry

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Abstract

Objective

Schnitzler syndrome (SchS) is a rare autoinflammatory disease characterised by a primary pathogenic involvement of interleukin (IL)-1. Therefore, IL-1 blockers are currently considered the optimal therapeutic option for SchS patients. However, while IL-1 blockers are first-line for SchS, long-term real-world evidence is limited by the rarity of the disease. We assessed the long-term effectiveness and safety of the IL-1 inhibitors anakinra and canakinumab used in SchS, also looking for variables capable of affecting global effectiveness and drug retention over time.

Methods

Data analysed in this study were drawn from the international AutoInflammatory Disease Alliance (AIDA) Registry dedicated to SchS.

Results

28 SchS patients corresponding to 37 treatment lines were included in the study. Complete and partial responses occurred in 73.1% and 29.9% of anakinra-treated patients, and 66.8% and 33.3% with canakinumab. The overall anakinra and canakinumab drug retention rates at 12-, 36-, and 60-month follow-up were 85.6%, 81.7% and 64.7%, respectively; the probability of discontinuing IL-1 inhibitors at 12-, 36- and 60 months due to loss of effectiveness was 9.6%, 13.7% and 24.5%, respectively. The maximum IgG M-protein levels were found to be significantly higher in patients achieving partial response compared to those benefiting from complete response (p=0.032). Lymphadenopathy independently predicted anti-IL-1 discontinuation due to loss of effectiveness (HR 7.78, 95% CI: 1.27–47.9; p=0.027).

Conclusion

The present study confirms the high effectiveness of IL-1 inhibitors in controlling SchS, including the complete and partial response rates and the long-term survival. Elevated IgG M-protein levels and the presence of lymphadenopathy should be considered as potential indicators for identifying patients more likely to exhibit a partial response and a possible loss of treatment efficacy.

Key words

anakinra, autoinflammatory diseases, canakinumab, treatment, Schnitzler syndrome

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Introduction

Schnitzler syndrome (SchS) is a rare late-onset immune-mediated disease, currently considered to be sporadic, acquired and autoinflammatory in nature (1). Approximately 300 cases of SchS have been reported worldwide. Patients with SchS commonly experience a corollary of symptoms, encompassing recurrent fever, urticarial skin rash, arthritis and lymphadenopathy accompanied by IgM gammopathy (2, 3).

Despite its rarity, SchS is an important diagnosis to bear in mind, especially for dermatologists and all physicians dealing with recurrent fever episodes, as spontaneous remission of symptoms is unlikely and the impact on patients' lives is profound. Clinically, cutaneous lesions, mostly urticaria-like wheals, are usually the first sign of SchS and can precede other symptoms by years. The lesions are usually nonpruritic or only slightly itchy, resolve within 24 to 48 hours, and, invariably, antihistamines are ineffective. The frequency of urticaria-like skin changes ranges from daily to a few episodes per year. Histology of skin lesions reveals a neutrophilic infiltrate of the perivascular and interstitial dermis with neutrophilic epitheliotropism and no signs of vasculitis (4). The second most common symptom of SchS is intermittent fever, which can rise above 40°C. Furthermore, approximately 10% to 20% of SchS patients develop a clinically overt lymphoproliferative disorder such as Waldenström's macroglobulinemia or B-cell lymphoma. Many patients also develop bone pain and arthralgias, and bone lesions due to the aseptic inflammation can be observed in imaging studies. Laboratory signs of systemic inflammation, such as elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are typically present, together with leucocytosis, usually neutrophilia, and mild anaemia. Monoclonal gammopathy, mostly IgMκ light chain, is seen in 85% of Schnitzler syndrome patients, which is a characteristic feature of the syndrome that distinguishes it from cryopyrin associated periodic syndromes (CAPS).

Although in 2012 diagnostic criteria of SchS were defined, allowing a definite or probable diagnosis of the disease (5), it still remains highly underdiagnosed with a consequent delay of the initiation of specific treatment (6). Therefore, the final diagnosis relies heavily on a combination of clinical, laboratory and radiologic findings. Because skin lesions are almost always the earliest sign of the disease, dermatologists in the first instance should be prepared to consider the diagnosis of SchS in patients with recurrent episodes of hives-like skin lesions, fever, and bone and/or joint pain without evidence of infection or autoimmune disease.

The pathogenesis of SchS is complex and so far, not fully elucidated. However, it is now widely accepted that it shares the hallmarks of auto-inflammatory disorders (AIDs), as the innate immune system over activation, leading to increased production of interleukin-1 (IL-1) family members, and a 'sterile' neutrophil-rich cutaneous inflammation. Indeed, aberrant NLRP3 inflammasome signalling and IL-1 family pathway dysregulation have been shown to play a crucial role in SchS pathophysiology (7, 8). The emergence of new evidence supporting the autoinflammatory nature of SchS has paved the way for the investigation of IL-1 targeting agents for the treatment of the disease. Interestingly, anakinra, a recombinant IL-1 receptor antagonist, canakinumab, a monoclonal antibody selectively targeting IL-1β, and rilonacept, a dimeric fusion protein consisting of the ligand-binding domains of the IL-1 receptor linked to the Fc portion of human IgG1, are already approved for the treatment of CAPS, which closely resembles SchS. Anakinra and canakinumab are also used for Still's disease, another autoinflammatory condition bearing striking resemblances to SchS. To date, no IL-1-blocking agents have yet been specifically licensed for the extremely rare indication of SchS.

Nevertheless, a number of studies have already described good clinical responses with the IL-1 blockers anakinra, rilonacept and canakinumab in SchS (9-15). Among others, a 9-month trial in Schnitzler's syndrome conducted by de Koning *et al*. in 2013 dem-

onstrated good efficacy and an optimal safety profile with canakinumab 150 mg/month administered for 6 months, followed by a 3-month observation period (14). However, data regarding the long-term effectiveness and safety of these agents in a real-world setting are still scarce, particularly regarding the use of canakinumab at 300 mg/month. Aim of this study was to evaluate and analyse an international multicentre cohort of patients with Schnitzler's syndrome, extrapolated from the Autoinflammatory Disease Alliance (AIDA) International Registry, and treated with two IL-1 targeting agents, anakinra and canakinumab. We assessed the role of anti-IL-1 agents in terms of long-term effectiveness and hypothesised that specific disease manifestations, including lymphadenopathy or IgG M-protein levels could predict anti-IL-1 effectiveness.

Methods

Study design and participants

This study was based on retrospectively collected data from the International AIDA Network Registry dedicated to SchS. Methods and tools employed for patients' enrolment and data collection have been previously described (16). The enrolment of SchS patients in the AIDA Registry started in January 2021 and information on 28 patients up to December 2023 was extrapolated. ShcS was diagnosed according to the fulfilment of Strasbourg diagnostic criteria for Schnitzler's syndrome (5). The following data were collected for each patient: gender, age at disease onset and at diagnosis, duration of SchS, comorbidities, clinical characteristics, diagnostic scores and criteria of SchS and treatments undertaken. The primary aims of the study were to evaluate the effectiveness of two anti-IL-1 agents, anakinra and canakinumab, in our patient cohort by examining: (i) the drug survival and retention rates (DRRs) for both agents, taken together and separately, using Kaplan-Meyer survival curves for any reason for discontinuation (overall drug survival), and for loss of effectiveness only, and (ii) the percentages of patients who achieved complete response (CR) and partial response (PR) with each drug. Secondary aims were to evaluate whether variables including clinical features of SchS patients, disease duration, laboratory findings and concomitant treatments with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) could influence either the DRR or global effectiveness (measured in terms of CR and PR) of anakinra and canakinumab. Drawing on criteria from Simon *et al*. (5) and de Koning *et al*. (14), CR was defined as the absence or minimal presence of clinical disease activity, accompanied by normalisation of CRP levels and leukocyte counts. PR was defined as a marked clinical improvement, as reported by both the patient and the physician, along with a reduction of more than 75% in CRP levels from baseline, although still remaining above the normal range. Loss of effectiveness was defined as a combination of physician global assessment and worsening of clinical symptoms, accompanied by an increase in inflammatory markers, particularly CRP and leukocyte count, following an initial clinical benefit with anakinra or canakinumab.

Table I. Demographic and clinical features of our cohort of patients.

	Overall (n=28) no. of patients
Demographic characteristics at baseline	
Age at diagnosis, mean (SD)	55.04 (14.02)
Age at onset, mean (SD)	50.91 (14.87)
Age at baseline, mean (SD)	60.66 (13.56)
Female, n (%)	14 / 28 (50)
Disease duration at baseline (years), mean (SD)	4.12 (4.96)
Clinical characteristics at baseline	
Fever during attacks (°C), mean (SD)	38.66 (1.07)
Thoracic pain, n (%)	4 / 28 (14.3)
Skin manifestations	
Urticarial skin rash, n (%)	4 / 28 (14.3)
Cellulitis-like skin rash, n (%)	1 / 26 (3.8)
Erythematous skin rash, n (%)	3 / 26 (11.5)
Maculopapular skin rash, n (%)	1 / 26 (3.8)
Plantar psoriasis-like lesions, n (%)	1 / 26 (3.8)
Angioedema, n (%)	3 / 14 (21.4)
Lymphadenopathy, n (%)	3 / 24 (12.5)
Laterocervical lymph nodes, n (%)	2 / 24 (8.3)
Axillary lymph nodes, n (%)	1 / 24 (4.2)
Mesenterial/abdominal lymph nodes, n (%)	1 / 24 (4.2)
Splenomegaly, n (%)	2 / 15 (13.3)
Hepatomegaly, n (%)	1 /14 (7.1)
Pericarditis, n (%)	2 / 28 (7.1)
Pleuritis, n (%)	1 / 28 (3.6)
Abdominal pain, n (%)	2 / 28 (7.1)
Myalgia, n (%)	19 / 28 (67.9)
Arthralgia, n (%)	24 / 28 (85.7)
Arthritis, n (%)	3 /28 (10.7)
Bone pain, n (%)	9 / 14 (64.3)
Conjunctivitis (%)	1 /28 (3.6)
Aseptic osteomyelitis (%)	4 / 28 (14.3)
Peripheral nervous system involvement (%)	1 / 9 (11.1)
Complications, n (%)	
Amyloidosis, n (%)	2 / 28 (7.1)
Multiple myeloma, n (%)	2 / 28 (7.1)
Splenic marginal zone lymphoma with bone marrow invasion, n (%)	1 / 28 (3.6)
Comorbid diseases at baseline, n (%)	
Gastrointestinal comorbidities, n (%)	8 / 28 (28.57)
Hypertension, n (%)	7 / 28 (25.00)
Hypercholesterolaemia, n (%)	5 / 28 (17.85)
Osteoporosis, n (%)	5 / 28 (17.85)
Diabetes II, n (%)	4 / 28 (14.28)
Cardiovascular comorbidities, n (%)	4 / 28 (14.28)
Haematological comorbidities, n (%)	3 / 28 (10.71)

n: number; SD: standard deviation.

Protocol approval

The Ethics Committee of the Azienda Ospedaliero-Universitaria Senese, Siena, Italy approved the study (institutional review board number: 14951; NCT05200715), as part of the AIDA programme. It was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consent to participate in the international AIDA Registry for SchS patients was obtained from all patients and/or their legal guardian. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU).

Statistical analysis

Descriptive statistics included mean and standard deviation (SD), and median and interquartile range (IQR) for continuous variables, while frequency and percentages were reported for categorical variables. For qualitative data, comparisons were performed using the Chi-square test or Fisher's exact test, depending on the number of samples. For quantitative data, the Student's t-test or Mann-Whitney U-test was used for pairwise comparisons, as required. Overall, DRRs at 12, 36 and 60 months were examined using Kaplan-Meier survival analysis taking into account: (i) any reason for discontinuation (overall drug survival) and (ii) only "loss of effectiveness". Univariate Cox regression was used to estimate hazard ratios (HRs), their 95% confidence intervals (95% CIs) and corresponding p values were calculated for each factor considered. Sensitivity analyses were conducted to ensure robustness of results. A $p<0.05$ was considered statistically significant. All data were assessed using the software R version 4.1.0.

Results

In total, 28 patients were included in the study. Demographic and clinical features of SchS patients are summarised in Table I. Laboratory analysis showed that 8 subjects had an IgG monoclonal gammopathy, while IgM monoclonal gammopathy was detected in 20 patients. Table II details previous and concomitant treatments of SchS patients. All patients in our cohort received anakinra (n=28) as first-line biologic agent, among them 9 subjects were treated with canakinumab thereafter. In total, csDMARDs had been administered in 22 patients, and 5 received concomitant treatment with anti-IL-1 agents and csDMARDS consisting of colchicine in 3 cases and methotrexate in 2 cases. Lastly, 28 subjects received corticosteroids during their clinical history, among whom 21 were on treatment at the start of anti-IL-1 agents, while 11 patients were treated with non-steroidal anti-inflammatory drugs.

Table II. Past and current treatments in our cohort of patients.

Past and current treatments	
Daily NSAIDs, n (%)	6 / 28 (21.4)
NSAIDs on demand, n (%)	5 / 28 (17.9)
Corticosteroids, n (%)	28 / 28 (100.0)
Daily acetaminophen, n (%)	1 / 28 (3.6)
Acetaminophen on demand, n (%)	3 / 28 (10.7)
Antihistamines, n (%)	17 / 28 (60.7)
Colchicine, n (%)	8 / 28 (28.6)
Azathioprine, n (%)	2 / 28 (7.1)
Cyclosporine A, n (%)	5 / 28 (17.9)
Dapsone, n (%)	3 / 28 (10.7)
Methotrexate, n (%)	10 / 28 (35.7)
Mycophenolate mofetil, n (%)	2 / 28 (7.1)
Anakinra, n (%)	26 / 28 (92.9)
Canakinumab, n (%)	9 / 28 (32.1)
Rituximab, n (%)	1 / 28 (3.6)
Tocilizumab, n (%)	3 / 28 (10.7)
Intravenous immunoglobulins, n (%)	1 / 28 (3.6)

n: number; NSAIDs: non-steroidal anti-inflammatory drugs.

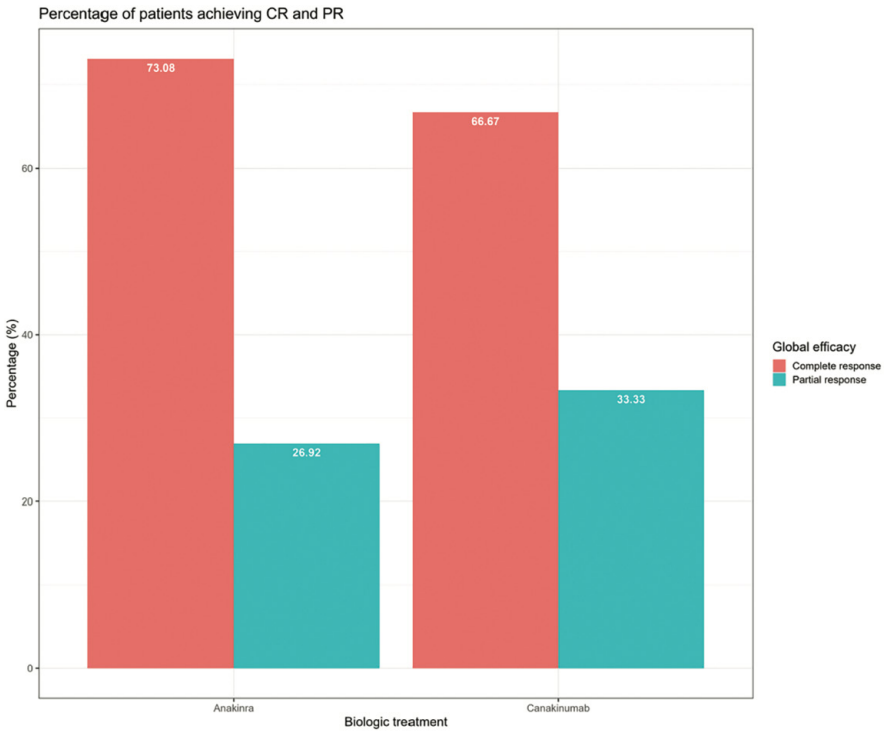

Fig. 1. Global efficacy. Percentage of patients achieving complete and partial response with anakinra and canakinumab. No significant differences between the two biotechnological agents were detected.

Treatment response in terms of global effectiveness

In total, 37 treatment lines with the IL-1 inhibitors anakinra and canakinumab were administered to the 28 enrolled patients. In two out of the 37 treatment lines, it was not possible to evaluate

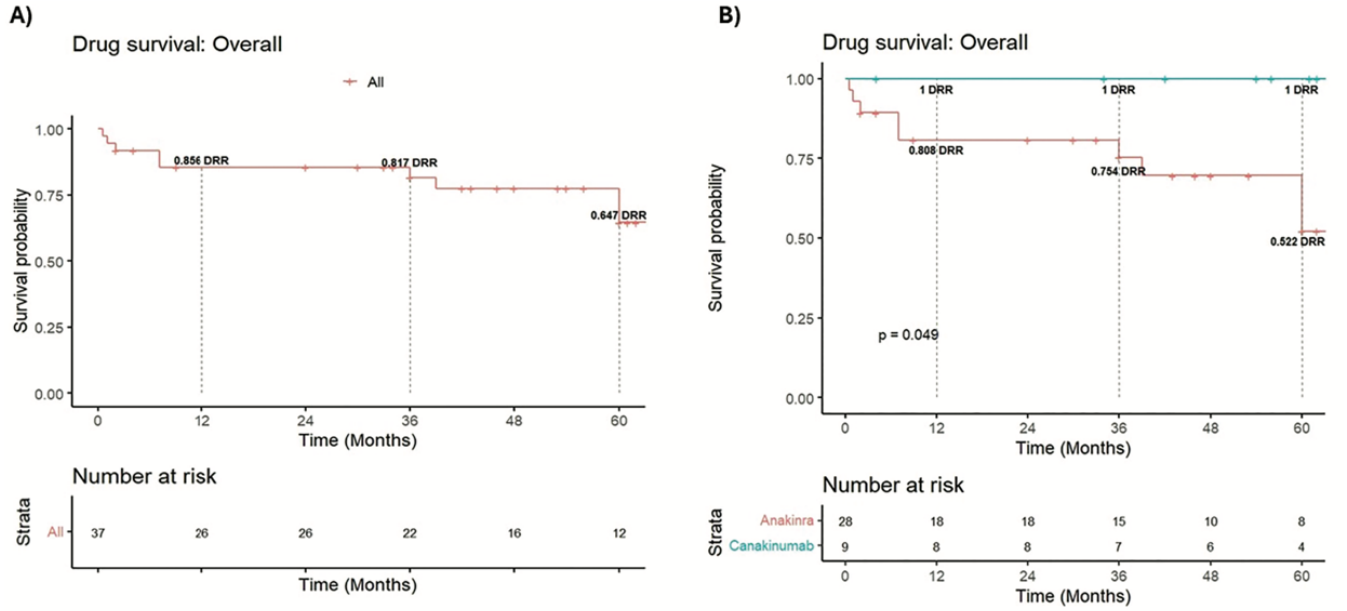

Fig. 2. Overall anti-interleukin treatment survival. Kaplan-Meier survival curve showing the overall survival related to any reason for discontinuation (loss of efficacy, adverse events, other non-medical reasons) of anakinra and canakinumab taken together (**A**) and separately (**B**).
DRR: drug retention rate.

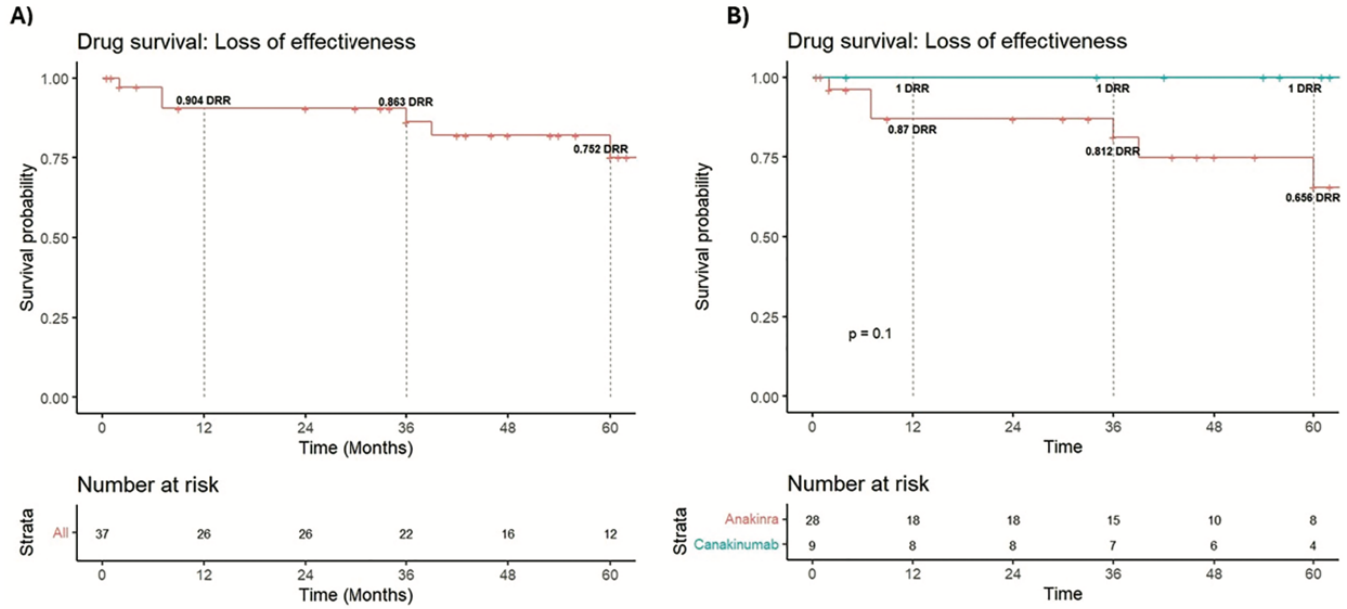

Fig. 3. Drug survival related to loss of effectiveness. Kaplan-Meier survival curve showing the survival related to the loss of effectiveness as event leading to treatment discontinuation of anakinra and canakinumab taken together (**A**) and separately (**B**).
DRR: drug retention rate.

the global effectiveness of the drugs in terms of CR and PR. Indeed, these two patients experienced an adverse event (AE) during anakinra treatment, consisting of injection site reaction in both cases, leading to drug discontinuation as early as the first month of treatment. Conversely, no AEs causing withdrawals were reported during treatment with canakinumab. The percentage of patients achieving CR and PR were 73.1% and 29.9% for anakinra and 66.8% and 33.3% for canakinumab, respectively, with no significant differences between the two groups (p=0.694) (Fig. 1). When looking for clinical or laboratory differences between patients experiencing CR and those showing PR, a significantly higher maximum IgG M-protein levels were found in patients who achieved a PR with anti-IL-1 agents, compared to those who achieved a CR (p=0.032). In particular, the mean (SD) of the highest recorded IgG M-protein levels was 789.56 (600.42) mg/dL in patients who achieved complete remission, compared to 6750.00 (8838.83) mg/dL in those with a partial response (Supplementary Table S1).

Drug retention rates

The Kaplan-Meier survival curves, differentially considering any reason for

discontinuation (overall DRR) and only loss of effectiveness are shown in Figures 2 and 3, respectively. In the drug-survival analysis, 9 events leading to anakinra discontinuation were detected (n=6 loss of effectiveness, n=2 AEs, and n=1 drug withdrawal due to non-medical reasons). The median treatment duration of anakinra and canakinumab taken together, was 32 (IQR=48) months and 39 months (IQR=19.5), respectively. The overall DRRs of both agents at the 12-, 36-, and 60-month follow-up were 85.6%, 81.7% and 64.7%, respectively (Fig. 2A). While the DRRs of canakinumab only remained constant (100%) throughout the study period, the anakinra DRRs were 80.7%, 75.4% and 52.2% at 12, 36, and 60 months of follow-up, respectively (Fig. 2B). These differences achieved a statistic significance (log-rank *p*-value= 0.049).

Besides, when considering only loss of effectiveness as a discontinuation reason of both IL-1 antagonists, DRRs at 12-, 36-, and 60-months of follow-up resulted in 90.4%, 86.3% and 75.5%, respectively (Fig. 3A). Consequently, the probability of discontinuing IL-1 inhibitors at 12, 36 and 60 months due to loss of effectiveness was 9.6%, 13.7% and 24.5%, respectively. The canakinumab DRRs related to the loss of effectiveness remained constant during the whole follow-up, while the anakinra DRRs were 87%, 81.2% and 65.6% at 12, 36, and 60 months of follow-up, respectively (Fig. 3B).

Regarding the overall DRRs for both IL-1 inhibitors taken together, none of the parameters analysed in our cohort were found to significantly influence the overall survival of IL-1 inhibitors at univariate Cox regression (Suppl. Table S2).

Table III provides results pertaining to the variables analysed using univariate Cox regression analysis, that could possibly affect the treatment survival of anakinra and canakinumab together related to loss of effectiveness, including disease duration, laboratory parameters, concomitant csDMARDs use, and baseline disease manifestations. In detail, the presence of lymphadenopathy was identified as the only predictor of IL-1 inhibitors discontinuation due to loss of effectiveness at univariate Cox regression analysis [HR 7.78 (CI: 1.27–47.9), *p*=0.027] (Suppl. Fig. S1).

Table III. Univariate Cox regression analyses to assess potential variables associated with the persistence of interleukin-1 inhibitors, with the loss of effectiveness being the reason for discontinuation.

Item	Treatment line performed	HR	95% CI	*p*-value
Thoracic pain	37	1.17	0.14, 10.0	0.89
Urticarial skin rash	37	0.45	0.05, 3.90	0.47
Other types of skin rash	35	0.76	0.09, 6.62	0.80
Erysipelas-like	35	3.59	0.41, 31.2	0.25
Erythematous	35	1.14	0.13, 9.95	0.91
Maculopapular	35	0.00	0.00, Inf	0.99
Angioedema	18	2.33	0.14, 38.7	0.56
Lymphadenopathy	32	7.78	1.27, 47.9	0.027
Splenomegaly	20	4.18	0.26, 67.6	0.31
Hepatomegaly	18	7.25	0.45, 116	0.16
Pericarditis	37	3.45	0.39, 30.2	0.26
Pleuritis	37	3.77	0.43, 32.8	0.23
Myalgia	37	0.67	0.12, 3.75	0.65
Arthritis	37	1.41	0.16, 12.1	0.75
Conjunctivitis	37	4.31	0.48, 38.7	0.19
Aseptic osteomyelitis	37	1.72	0.20, 14.8	0.62
csDMARD concomitant	37	2.11	0.38,11.8	0.39
Colchicine concomitant	37	1.53	0.18,13.2	0.70
Methotrexate concomitant	37	2.41	0.27,21.6	0.43
Disease duration, mean (SD)	33	1.00	0.99, 1.01	0.83
ESR mm/1h, mean (SD)	25	0.99	0.89, 1.09	0.79
Max ESR, mm/1h (mean (SD))	25	0.96	0.89, 1.05	0.38
CRP, mg/dl (mean (SD))	28	1.02	1.00, 1.05	0.075
Max CRP, mg/dl (mean (SD))	28	1.01	0.99, 1.04	0.25
IgG M-protein, mg/dl (mean (SD))	11	0.45	0.00, 2,183	0.85
Max IgG M-protein, mg/dl (mean (SD))	11	0.69	0.20, 2.34	0.55
IgM M-protein, mg/dl (mean (SD))	33	1.00	0.99, 1.01	0.83
Max IgM M-protein, mg/dl (mean (SD))	25	0.99	0.89, 1.09	0.79

CRP: C-reactive protein; CI: confidence interval; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HR: hazard ratio; IgG: immunoglobulin G; IgM: immunoglobulin M; M-protein: myeloma protein; SD: standard deviation.

Discussion

Although internationally accepted guidelines for treatment of SchS have not been published so far, the treatment algorithm used for these patients include colchicine as first-line treatment and IL-1 inhibiting agents in difficult-to-treat cases. In this regard, the efficacy of IL-1 antagonists is as affective that their failure should induce diagnosis reconsideration (17). Indeed, the rationale for using anakinra and canakinumab to treat SchS is based on emerging and robust evidence supporting the IL-1 mediated autoinflammatory nature of the disease. Indeed, it has been reported that peripheral blood mononuclear cells (PBMCs) from SchS patients release increased amounts of IL-1β, both spontaneously and in response to lipopolysaccharide (8). Moreover, high levels of the inflammasome component ASC (the adaptor molecule apoptosis-associated speck-like protein containing a CARD), and of the cytokines IL-6 and IL-18 have been demonstrated in serum of patients with SchS compared to controls (18) and an hyperproduction of IL-1β has been detected in mastocytes of both lesional and non-lesional skin of patients with SchS (19). Furthermore, there are strong clinical similarities between SchS and a number of prototypic monogenic autoinflammatory disorders, like CAPS, which are caused by gain of function mutations in *NLRP3*, the gene encoding NLRP3, also known as cryopyrin, a component of the NLRP3 inflammasome (20). Interestingly, some SchS patients have indeed shown to have a mosaicism of *NLRP3* mutations, restricted to the cells of myeloid lineage (2, 21), although recent studies using next-generation sequencing (NGS) approach have not confirmed those results (18). Indeed, it has been theorised that

a population of myeloid cells with an acquired *NLRP3* mutation may produce abnormally high quantities of IL-1β, inducing chronic stimulation and clonal expansion of local B cells expressing IgM or, less commonly, IgG, implying that the M-protein might be a by-product of inflammation rather than a pathogenic trigger (21).

Furthermore, one-third of SchS patients showed somatic gain-of-function mutation in *MYD88* (L265P) (22). MYD88 gene encodes a cytosolic adapter protein, myeloid differentiation primary response 88 (MYD88), essential for transducing the signal downstream of several receptors of the IL-1 family (23, 24). Interestingly, MYD88 (L265P) mutation has also been reported in more than 90 percent of Waldenström's macroglobulinemia patients, underscoring the link between this latter and SchS (25).

Among the IL-1 targeting agents, both anakinra and canakinumab have been already approved for the treatment of CAPS, and canakinumab also for Still's disease, with both conditions sharing similar clinical features with SchS (23). Several studies have previously examined the effectiveness and safety of IL-1 inhibitors in SchS, including a former report by our group (9-14, 26). Néel *et al*. reported that, based on 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. As regards safety, 5 patients (17%) suffered from injection site reaction, with no need of suspending the treatment (9). Furthermore, Rowczenio *et al*. reported that 95% of 20 patients with SchS experienced the disappearance of all symptoms during anakinra treatment (18).

Similar to anakinra, canakinumab has been reported to be effective in the disease control as well. In detail, a phase II, randomised, placebo-controlled multicentre trial, investigated the use of canakinumab in 20 patients with active SchS. The proportion of patients achieving the primary endpoint of complete clinical response at day 7 was significantly higher in the canakinumab-treated group than in the placebo group and levels of inflammation markers (CRP and serum amyloid A) were significantly reduced in the canakinumab-treated arm. These effects were sustained for up to 16 weeks. AEs included respiratory tract infections, gastrointestinal symptoms, and hypertension (12). Results from the extension phase of the same trial confirmed sustained effects over 4 years of treatment (13).

Lastly, our group conducted a retrospective study in 2021, focusing on the DRRs of both anakinra and canakinumab on 15 SchS patients, which was reported to be 73.4% at 1 year and 63.6% at 2 years, with no significant differences between the two agents. At the last follow-up visit, all patients receiving IL-1 inhibitors were still on treatment and a sparing effect on the use of csDMARDs as well as a significant reduction of prednisone dosage and of serum amyloid A levels were observed (26).

The present study is the first to be based on data retrieved from the international AIDA registry, specifically dedicated to patients with SchS, which was designed, developed, and is continuously implemented in order to promote dissemination of knowledge, and shed light on many blind spots characterising this complex autoinflammatory disorder (16).

In the present study, beyond confirming the long-term effectiveness of anti-IL-1 therapy with anakinra and canakinumab in terms of clinical response and DRR, we also identified specific clinical features potentially associated with reduced treatment efficacy or loss of effectiveness. In particular, this study has firstly shown that the presence of lymphadenopathy and IgG M-protein serum levels are predictive of a suboptimal response.

More in detail, in this study treatment with two anti-IL-1 agents, anakinra and canakinumab, inhibiting IL-1α/β and IL-1β only, respectively, has proven good effectiveness as first or subsequent line biological DMARDs (bDMARDS). In particular, none of the patients experienced a lack of effectiveness, at least a PR was observed in all subjects enrolled, and most of the patients achieved a complete clinical response. When considering anakinra and canakinumab together, the overall drug survival and the survival related to loss of effectiveness corresponded to 64.7% and 75.5% at 5 years from the start of treatment, respectively, further highlighting the optimal role of IL-1 inhibitors even in the long-term. When considering anakinra and canakinumab separately, a statistically significant difference in overall survival favoured canakinumab. However, this significance disappeared when evaluating survival related specifically to loss of effectiveness. Therefore, the significant difference was likely to be attributed to factors other than loss of effectiveness, including AEs and non-medical reasons. These findings differ from the results previously reported by Crisafulli *et al*. (26), who did not identify any statistically significant difference in the DRRs of anakinra and canakinumab. This discrepancy is likely due to the larger sample size collected in the present study and the different duration of follow-up. Furthermore, the AEs that led to the discontinuation of anakinra were primarily injection site skin reactions. These reactions, although bothersome, were not severe enough to complicate the overall clinical picture or pose significant health risks to the patients. Consequently, the decision to discontinue anakinra was influenced more by the inconvenience caused by these reactions rather than any serious medical complications.

Interestingly, it was not possible to demonstrate that anakinra and canakinumab achieved a statistically different clinical outcome in terms of frequency of CR and PR. Based on this result, one might possibly theorise that blockade of IL-1β is sufficient to achieve adequate control of the disease. Nevertheless, the relatively low number of treatment courses with canakinumab in the study does not allow for a robust comparison between the two therapeutic agents and therefore to draw definitive conclusions. Many clinical, laboratory, and treatment parameters, including serum levels of the M-protein, patients' clinical manifestations, disease duration at treatment onset, any concomitant use of csDMARDs, and markers of systemic inflammation such as CRP and ESR, have been investigated as possible factors capable of affecting drug effective-

ness and drug survival. Interestingly, a statistically significant relation was found between maximum IgG M-protein levels and percentage of patients achieving a PR, suggesting that high IgG M-protein levels, and not IgM, the most common type of M-protein in SchS, may be a negative predictor of response to IL-1 inhibitors. Based on the literature data, we cannot provide explanations for the reasons why this result occurred, but this could be further clarified by experimental studies in the future. One possible explanation for the association between lymphadenopathy and treatment failure may involve broader immune activation or cytokine spill-over beyond the IL-1 pathway in such cases, suggesting that in certain patients, more complex or redundant inflammatory mechanisms are at play. Noteworthy, in a Japanese case-collection report the serum IgM levels were found to be gradually increased in all patients treated with IL-1 or IL-6 antagonists. However, IgG levels were not mentioned so far, and our finding deserves to be further investigated and confirmed on wider cohorts (27).

Except for lymphadenopathy, which significantly correlated with loss of effectiveness of anti-IL-1 agents, no specific clinical manifestations, including any type of skin lesion, showed a significant impact on drug survival. Therefore, a generalised lymphadenitis should prompt physicians to pay closer attention to patients, as they seem to be more likely to experience a loss of effectiveness over time.

As regards the safety profile, our data confirmed previous studies that reported a high tolerability of IL-1 inhibitors (15): indeed, in our cohort, anakinra was withdrawn in only 2 patients, in both cases due to injection site reactions.

In our cohort, two patients developed multiple myeloma and one splenic marginal zone lymphoma with bone marrow invasion as complications of SchS. So far, only one case of SchS associated with systemic marginal zone lymphoma has been described in the literature (28). Cutaneous manifestations of SchS have been thoroughly explored and as expected, the great majority of patients had an urticaria-like skin rash. However, one patient developed plantar psoriasis-like lesions. Interestingly, a case of anakinra-induced psoriasis has been reported in one patient with SchS. In this regard, it still remains to be clarified whether an association between psoriasis and SchS might exist (29). Of note, most patients included in this study suffered from chronic urticarial skin rash, but other sporadic skin manifestations were also observed. These may either represent inflammatory skin manifestations of SchS or incidental findings; this open question should be faced in further studies and supported by histologic findings.

Our study suffers from some limitations, including the limited number of patients and the relatively short follow-up period. In particular, we acknowledge that the relatively small sample size may reduce the statistical power and increase the risk of type II error. This limitation may have hindered the detection of potentially meaningful associations, and thus our findings should be interpreted with caution and validated in larger cohorts. In addition, we considered inappropriate to conduct a Cox regression analysis based on drug survivals of anakinra and canakinumab separately, as this would not yield robust data owing to the small sample sizes. Finally, this is a registry-based study with an open, retrospective and multicentre design. Therefore, potential biases such as missing data and selection bias must be acknowledged. Also, data collection may be influenced by variations in clinical practice, and the inclusion of patients enrolled in a registry may not fully reflect the broader population affected by the disease. Nevertheless, our observations confirm the long-term efficacy of IL-1 inhibitors in controlling clinical manifestations and reducing inflammation in patients with SchS, as reflected by the high rates of CR and DRRs, the latter even higher than those in our previous report, as well as their excellent safety profile. In particular, the results of this study support the need for thorough baseline assessment before initiating anti-IL-1 therapy, in order to identify patients potentially at higher risk of loss of efficacy or inadequate clinical response. These individuals may warrant more intensive follow-up and closer monitoring throughout the treatment course.

In conclusion, our study further reveals the high effectiveness of IL-1 inhibitors in controlling SchS. It demonstrates, no correlation between specific clinical manifestations, including any type of skin lesion, and response to anti-IL-1 agents or drug survival, with the exception of lymphadenitis and IgG M-protein levels, possibly useful in identifying patients requiring closer follow-up. Prospective studies on larger cohorts of SchS patients should be encouraged in order to thoroughly characterise response patterns and accurately identify possible factors influencing response to IL-1-targeted agents in SchS.

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