Rheumatology International (2019) 39:971–990
https://doi.org/10.1007/s00296-019-04259-y

Rheumatology
INTERNATIONAL

SYSTEMATIC REVIEW

The right place of interleukin-1 inhibitors in the treatment of Behçet's syndrome: a systematic review

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Received: 9 January 2019 / Accepted: 16 February 2019 / Published online: 25 February 2019

Abstract

Behçet's syndrome (BS) is a chronic (auto)-inflammatory disorder characterized by different clusters of symptoms, including mucocutaneous and ocular involvements. Interleukin-1 inhibitors anakinra (ANA), canakinumab (CAN), and gevokizumab (GEV) represent a promising therapeutic alternative in BS. To date, evidence on the use of ANA, CAN, and GEV is mainly based on small isolated studies or case series, and the real place of anti-IL1 agents in the treatment of BS is still unclear. We performed a systematic review of current evidence on the efficacy and safety of anti-IL1 agents in BS. The PubMed search yielded a total of 398 references, from which we retrieved 24 studies for inclusion (4 clinical trials, 6 observational studies, 14 case reports, case series or letters to the editor). Four studies evaluated the overall efficacy of IL-1 inhibitors, 15 studies focused on the specific efficacy of ANA, whereas efficacy of CAN and GEV was evaluated in 8 and 3 studies, respectively. Both ANA and CAN were associated with good control of mucocutaneous and ocular manifestations. ANA resulted effective also for osteoarticular manifestations. GEV was studied only for ocular manifestations, but gave contrasting results. Discordant evidence supports the use of ANA and CAN in pediatric setting and for first-line treatment of general BS manifestations. Most frequent side effects were local or diffuse cutaneous reactions and injection site reactions, particularly for ANA treatment. Blocking the IL-1 pathway could be an effective therapeutic strategy in particular BS involvements.

Keywords Interleukin-1 · Anakinra · Canakinumab · Gevokizumab · Behçet's syndrome

Introduction

Behçet's syndrome (BS) is a chronic (auto)-inflammatory disorder characterized by a complex pathogenesis [1–10]. Main BS involvements include recurrent oral aphthosis, genital ulcers, cutaneous lesions, and ocular inflammatory manifestations [1, 11].

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-019-04259-y) contains supplementary material, which is available to authorized users.

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According to the 2018 European League Against Rheumatism (EULAR) recommendations [12], therapeutic approach to BS should be tailored to specific disease manifestations. Current treatment relies mainly on synthetic disease-modifying anti-rheumatic drugs (DMARDs), and on biologic agents, particularly anti-tumor necrosis factor (TNF)-α drugs [13–23]. When conventional immunosuppressive and anti-TNFα agents are ineffective, treatment of BS relies on new therapeutic alternatives, targeting key molecules such as the interleukin (IL)-6 [24, 25], or blocking the IL-17 pathway [26, 27]. More recently, evidence suggests that the IL-1 inhibitors anakinra (ANA), canakinumab (CAN), and gevokizumab (GEV) may play a relevant role in other therapeutic indications including BS [28–31].

ANA is the recombinant form of the natural IL-1 receptor antagonist (IL-1Ra), and acts by preventing the binding of IL-1α and IL-1β to IL-1R1 [32]. On the other hand, CAN is a recombinant human monoclonal antibody specifically targeting IL-1β [33]. GEV is a recombinant humanized allosteric monoclonal antibody that specifically binds to a unique IL-1β epitope, thus neutralizing IL–1β and inhibiting its activation of the IL-1 receptors [34]. ANA and CAN are currently approved for the treatment of rheumatoid arthritis, familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome, Still's disease and gout arthritis, while GEV has no specific indications at present.

However, the real place of anti-IL1 agents in the treatment of BS is still unclear. In this context, this systematic review aims to provide an overview of published articles and to summarize evidence on the efficacy and safety of anti-IL1 agents ANA, CAN, and GEV on the management of BS.

Materials and methods

Criteria for considering studies

Given the small number of clinical trials and observational studies on this topic, all types of original studies were considered, including clinical trials, observational studies, case series, case reports, and letters to the editor. Narrative and systematic literature reviews and meta-analysis were excluded. Only studies written in English were considered, independently from the date of publication. Studies performed on either pediatric or adult patients with a BS diagnosis were considered; BS diagnosis was defined either as fulfillment of ISG/ICBD criteria for BS or based on authors' definitions. Only studies on ANA or CAN or GEV were included, independently from the treatment regimen.

All reported data on either efficacy or safety were considered. Definitions used for both response achievement and adverse events were those reported by the authors of the studies.

Search methods for identification of studies

The PubMed and Embase databases were searched from inception to January 14th 2019. The literature search strategy used for PubMed is "(Anakinra*[tiab] OR Canakinumab*[tiab] OR XOMA 052*[tiab] OR Gevokizumab*[tiab] OR Interleukin 1 inhibitor*[tiab] OR "Interleukin 1 Receptor Antagonist Protein"[Mesh] OR "canakinumab" [Supplementary Concept] OR "gevokizumab" [Supplementary Concept]) AND (Behcet*[tiab] OR "Behcet Syndrome"[Mesh] OR (safety[tiab] AND clinical practice[tiab]) OR off label[tiab] OR desensitization*[tiab])". The literature search strategy used for Embase is "(Anakinra*:ti,ab OR Canakinumab*:ti,ab OR XOMA 052:ti,ab OR Gevokizumab*:ti,ab OR Interleukin 1 inhibitor*:ti,ab OR 'anakinra'/exp OR 'canakinumab'/exp OR 'gevokizumab'/exp) AND (Behcet*:ti,ab OR 'Behcet disease'/exp OR (safety:ti,ab AND clinical practice:ti,ab) OR off label:ti,ab OR desensitization:ti,ab)".

Data collections and analysis

Two review authors (AB and GE) independently identified studies for inclusion by screening titles and abstracts yielded by search. Articles were sought for all references that at least one of the review authors had identified for potential inclusion. Studies were selected for inclusion on the basis of the review of the full articles. Discrepancies were resolved through discussion. Two review authors (AB and GE) independently extracted the following data: (1) patients' demographic data; (2) clinical data (BS manifestations and comorbidities); (3) previous treatments and reasons for interruption; (4) treatment data (active principle and dosage); (5) outcome data (achievement of responses, adverse events, treatment discontinuation and reason); and (6) other data (study design; year of publication; country in which participants were recruited).

The risk of bias of the included controlled clinical trials was assessed following the Cochrane Handbook for Systematic Reviews of Interventions [35]. The risk of bias of observational studies was assessed following the Newcastle-Ottawa Quality Assessment Scale [36].For single arm interventional studies, case reports, case series or letters to the editor, assessment of the risk of bias was not performed.

Results

The reference flow is summarized in Fig. 1. 106 references were identified through electronic search of PubMed and 327 through electronic search of Embase. After

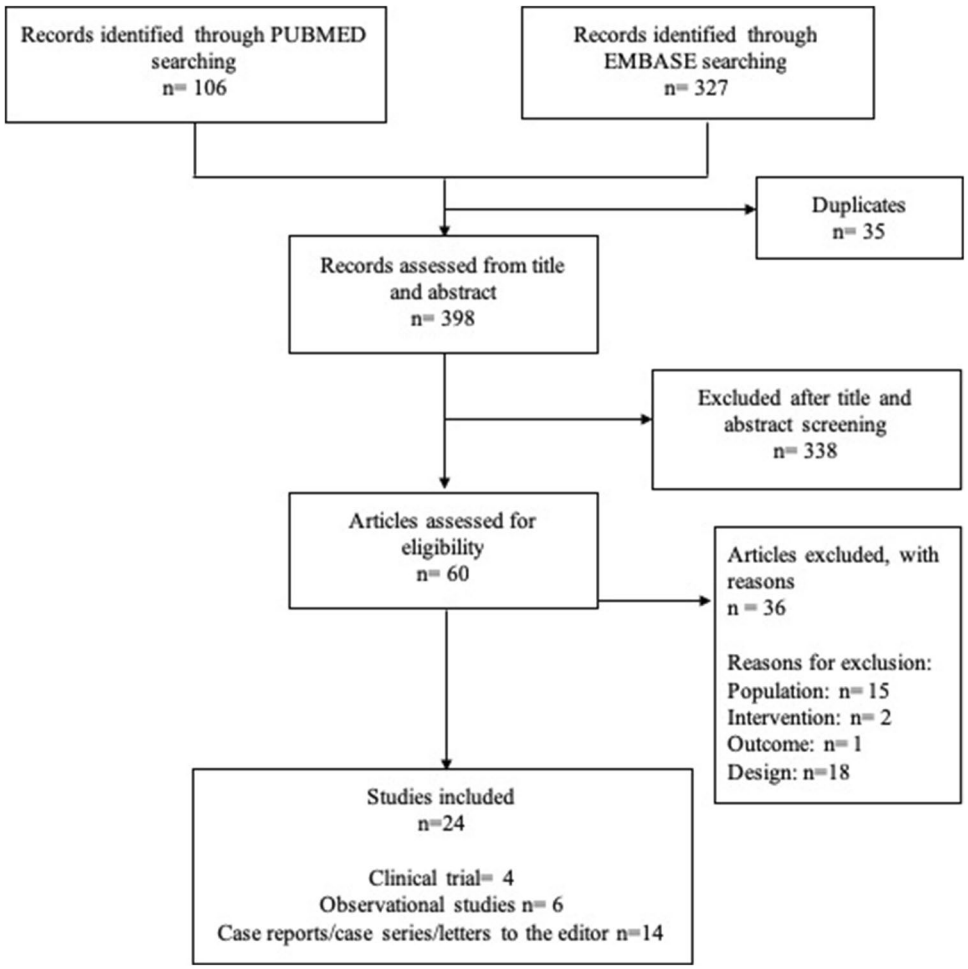

Fig. 1 Study flow diagram, retrieved on January 14th 2019

the removal of 35 duplicated records, 398 references were assessed by title and abstract. Of them, 338 were excluded, while 60 references were retrieved for further assessment. 36 references were excluded for the reasons listed in Fig. 1. In total, 24 references met the inclusion criteria [37–60]. Four studies were clinical trials (of these, three were controlled trials), six were observational studies, and 14 were case reports, case series or letters to the editor.

The quality assessment of the included clinical trials and observational studies is reported in Supplementary Table 1. The included clinical trial on ANA was judged at high risk of performance and detection bias, at unclear risk of selection bias (unclear risk for random sequence generation; low risk for allocation concealment), and at low risk of attrition and reporting bias [54]. One controlled trial on GEV [50] was judged at unclear risk of selection bias (unclear risk for random sequence generation; low risk for allocation concealment), and at low risk of performance, detection, attrition, and reporting bias. The other trial on GEV [51] was judged at high risk of performance and detection bias, and at low risk of selection, attrition, and reporting bias.

The included observational studies were of high quality, with two of them scoring 9/9 [38, 59], and four scoring 8/9 on the Newcastle-Ottawa quality assessment scale [37, 55, 56, 60].

The characteristics of the 24 included studies are summarized in Table 1. The main findings reported in the included studies are described in Table 2. Studies evaluating the efficacy of ANA and CAN on specific BS manifestations are reported in Fig. 2.

Overall efficacy of anti-IL1 inhibitors

Overall efficacy of IL-1 inhibitors, with no distinction between ANA and CAN, was reported in four studies [37, 55, 59, 60]. In a case–control study by Fabiani [37], use of ANA or CAN was associated with complete response in 25 out of 36 patients. Particularly, achievement of response was significantly more frequent in patients with BS-related uveitis (66.7% vs 16.7% of patients with uveitis among responders vs non-responders, respectively; $p = 0.006$), whereas presence of all other disease manifestations did not influence the achievement of the response. Among responders, relapse

Table 1 Characteristics of the 24 included studies

First author, year, reference	Study design	Population; clinically relevant characteristics	Interventions and dosage
Tugal-Tutkun, 2018 [50]	International, randomized, double-masked, placebo-controlled phase III study and open-label extension study	83 subjects; 60 male/23 female; age 34.7 ± 9.5 BS (ISGC) with uveitis involving the posterior segment (quiescent). Panuveitis ($n=52$), posterior uveitis ($n=31$). BCVA by ETDRS (letters) 71.2 ± 15.1; macular edema ($n=14$)	GEV 60 mg (every 4 weeks, subcutaneously) ($n=40$) or placebo ($n=43$), + standard corticosteroid tapering, + immunosuppressive therapy (mainly AZA and cyclosporine A)
Fabiani, 2018 [37]	Retrospective observational	36 subjects; 16 male/20 female; adult subjects (age 43.3 (± 14.4) and 41.1(± 11.5) in group 1 and 2 BS (ISGC and/or ICBD criteria). BS involvements requiring IL1 inhibition: ocular ($n=15$), articular ($n=20$), cutaneous ($n=7$), fever ($n=6$), gastrointestinal ($n=10$), vascular ($n=7$)	ANA ($n=26$), at the dose of 100 mg/day; CAN ($n=10$), at the dose of 150 mg/8 weeks (except 1 patient, 150 mg/6 weeks) Concomitant treatments: DMARDs ($n=15$), Corticosteroids ($n=31$)
Sota, 2018 [38]	Retrospective observational	475 subjects; 195 male /280 female; adult and pediatric (mean age at diagnosis 36.36 (± 22.18) years) BS ($n=46$) or other indication for use	ANA or CAN Starting dose of ANA: in adults 100 mg/day, (except in two cases; 200 mg/day), in children from 1 to 4 mg/kg/day Starting dose of CAN: in adults from 150 mg every 8 weeks to 300 mg every 4 weeks; in children dosages ranged from 2 mg/kg every 8 weeks to 5 mg/kg every 4 weeks Other concomitant treatments could be present
Vitale, 2017 [52]	Letter to the Editor	one subject, female, 30 years old BS (ICBD). History of recurrent oral and genital aphthosis, erythema nodosum, pseudofolliculitis and severe bilateral panuveitis; neuro-BS Eye involvement refractory to steroid and AZA	ANA (100 mg/day) Then, CAN (150 mg every 4 weeks)
Orlando, 2017 [49]	Letter to the Editor	One subject, male, 52 years old BS (ISGC) with bladder papillary cancer excision. 8-year history of bipolar aphthosis, erythema nodosum, lumbar pain, headache, severe recurrent uveitis with retinal vasculitis and severely impaired vision in his right eye. Positive HLA-B51 allele	ANA (at the dose of 100 mg/day, increased to 150 mg/day in order to obtain a complete control) CAN (150 mg/6 week). A low-grade, bladder papillary carcinoma was diagnosed short after CAN beginning
Grayson, 2017 [54]	Adaptive, two-phase clinical trial	6 adult subjects, 5 female/1 male, aged from 19 to 59 years BS (ISGC). Active mucocutaneous disease; on a stable or decreasing dose of steroids, NSAIDs, colchicine, or DMARDs for 4 weeks Organ involvement: cutaneous ($n=6$), musculoskeletal ($n=6$), gastrointestinal ($n=3$), ocular ($n=3$), vascular ($n=3$), and neurologic ($n=0$)	Initial treatment with ANA 100 mg daily via subcutaneous injections. If oral or genital ulcers persisted after the first month of treatment, ANA was increased to 200 mg daily. For patients with ulcers at month 6, ANA was further increased to 300 mg daily. At each study visit, CCSs could be decreased up to 20% of the total dose

Table 1 (continued)

First author, year, reference	Study design	Population; clinically relevant characteristics	Interventions and dosage
Fabiani, 2017 [55]	Retrospective observational study	19 subjects (7 m/12 female), mean age 44.10 (SD 17.08) years Adult BS subjects (ISGC) with refractory uveitis (monolateral 36.8%, bilateral 63.2%)	13 subjects treated with ANA 100 mg/day, 3 with CAN 150 mg every 6 weeks, 1 with CAN 150 mg every 4 weeks, 1 with CAN 150 mg every 8 weeks, and 1 with CAN 300 mg every 6 weeks Co-treatments: none (9), cyclosporine A (4), AZA (3), MTX (2), sulfasalazine (1), CCSs (15), colchicine (0)
Tugal-Tutkun, 2016 [51]	Prospective, open-label, randomized, parallel-group phase 2 trial	21 adult patients (16 male/5 female, age 34.0 ± 9.3 years) BS (ISGC) with new acute ocular exacerbation or at risk of exacerbation (17 acute and 4 at risk; mean duration of uveitis 45.6 ± 37.4 months). Panuveitis ($n = 18$), posterior uveitis ($n = 3$) BCVA by ETDRS (letters): 35.4 ± 22.7 in acute patients; 61.5 ± 21.3 in patients at risk. Retinal infiltrates ($n = 12$); retinal vasculitis ($n = 11$)	All patients initially received intravenous GEV 30 or 60 mg At the time of response, three arms: GEV 30 mg subcutaneous vs GEV 60 mg subcutaneous vs GEV 30 mg intravenous every 4 weeks
Vitale, 2016 [56]	Retrospective observational study	56 BS patients; 17 male/31 female; 1 pediatric patient. Mean age 39.54 ± 13.32 years (mean age at diagnosis 31.24 ± 12.41)	ANA: 41 subjects CAN: 15 subjects Co-treatments: Monotherapy 8/46; CCSs 19; DMARDs 7; CCSs + DMARDs: 22
Emmi, 2017 [57]	Letter to the Editor	Two subjects BS and previous severe delayed ISR to ANA Refractory diseases, unresponsive to other treatments One patient with FMF, the other with idiopathic non-infectious uveitis	ANA No CCSs and antihistamines use
Emmi, 2017 [58]	Case report	One man, 41 years old BS with concomitant latent tuberculosis infection History of recurrent oral aphthosis, genital ulcerations, and pseudofolliculitis History of monthly fever attacks. hip arthralgia, and abdominal pain with diarrhea without evidence of inflammatory lesions at colonoscopy	CCSs (6-methylprednisolone 500 mg/d intravenously for 3 consecutive days followed by shortly tapering oral prednisone until 5 mg/day) and ANA (100 mg/day subcutaneously)
Cantarini, 2017 [59]	Retrospective cohort study	85 treatment regiments (of whom 18 with ANA/CAN) BS (ISGC)	Biologics: anti-TNF-alfa, or ANA or CAN ANA was administered subcutaneously at the dosage of 100 mg once a day; CAN was administered subcutaneously at the dosage of 150 mg every 6 weeks
Emmi, 2016 [60]	Retrospective observational study	30 subjects, 18 female, mean age at onset 26.5 ± 11.5 years BS (ISGC). Involvements to start treatment: eye (12), neurological (2), gastroenteric (4), mucosal (17), cutaneous (9), vascular (1), joint (9), fever (4)	27 subjects: ANA subcutaneously 100 mg/day 3 subjects: CAN 150 mg every 6–8 weeks Concomitant DMARDs: 26

Table 1 (continued)

First author, year, reference	Study design	Population; clinically relevant characteristics	Interventions and dosage
Pagnini, 2015 [39]	Letter to the Editor	One boy, 9 years old. Age at onset: 5 years Juvenile BS with recurrent fevers, oral and genital ulceration, skin lesions, arthralgia and abdominal pain	ANA, initially at the dosage of 2 mg/kg/day, increased to 4 mg/kg/day After 19 months, switched to CAN (4 mg/kg every 28 days) for inefficacy
Emmi, 2014 [40]	Letter to the Editor	Two subjects, 26 and 39 years, 1 woman/1 man BS (ISGC) Case 1: recurrent oral ulcers, pseudofolliculitis, erythema nodosum and positive pathergy test; abdominal pain with diarrhea and hands, wrists and knees arthritis Case 2: recurrent oral aphthosis, erythema nodosum, bilateral retinal vasculitis with reduced visual acuity	Case 1: ANA 100 mg/day Case 2: CAN 150 mg/8 weeks
Caso, 2014 [41]	Letter to the Editor	One man, 36 years old BS (ISGC) Recurrent oral and genital ulcerations, pseudofolliculitis, severe bilateral panuveitis with retinal vasculitis and sacroiliitis. HLA-B51 positive After IFX failure: At magnetic resonance imaging, subchondral bone marrow oedema involving both sacroiliac joints, with associated sclerosis and erosions	ANA (100 mg/day)
Vitale, 2014 [42]	Case report	Three subjects, two female/one male, 20, 41 and 47 years of age Refractory BS (ISGC) Case 1: recurrent oral and genital aphthosis, erythema nodosum, pseudofolliculitis, granuloma annulare, arthritis involving the knees, ankles and wrists, long-lasting abdominal pain, chronic headache, recurrent fever episodes. HLA-B51 positive Case 2: 8-year history of recurrent oral and genital ulcerations, headaches, two previous episodes of anterior uveitis, abdominal pain, diarrhea and diffuse arthralgia, recurrent odd fever episodes. HLA-B51 positive Case 3: 4-year history of recurrent bipolar aphthosis, recurrent deep venous thrombosis, panuveitis involving the right eye (with an average of three episodes/year), headaches and arthritis involving the knees and ankles, recurrent fever episodes. HLA-B51 positive. Pseudofolliculitis involving the trunk, lower limbs and face	Case 1: ANA 100 mg/day. Interrupted after a few weeks for diffuse pruritic urticarial lesions Switch to CAN 150 mg every 8 weeks by subcutaneous injection Case 2: ANA 100 mg/day. Interrupted after 8 weeks for no symptoms improvement Switch to CAN 150 mg every 6 weeks by subcutaneous injection Case 3: ANA 100 mg/day + prednisone. Interrupted after 18 months for severe diffuse pruritic urticarial lesions Switch to CAN 150 mg every 6 weeks

Table 1 (continued)

First author, year, reference	Study design	Population; clinically relevant characteristics	Interventions and dosage
Cantarini, 2015 [43]	Case series	Nine subjects, four female/five male, 7–59 years BS subjects (ISGC), HLA-B51 positive, pathergy test negative; bipolar aphthosis plus other manifestations	ANA 100 mg/day: 8/9; ANA 2 mg/kg/day: 1/9 Concomitant use of Prednisone: 8/9 DMARDs: 1/9
Emmi, 2013 [44]	Letter to the Editor	One adult woman, 27 years old BS (ISGC) Recurrent oral and genital ulcers and pseudofolliculitis of the trunk, arthritis/arthralgia of knees, ankles and wrists and abdominal pain with diarrhea. Severe ocular involvement with bilateral retinal vasculitis and reduced visual acuity	ANA: 100 mg/day
Gül, 2012 [53]	Pilot study	Seven BS patients, six male/ one female, age 25–37 years BS with acute posterior or panuveitis and/or retinal vasculitis	GEV 0.3 mg/kg (single intravenous Infusion) + continued to receive 10 mg or less of prednisolone. Second dose of GEV (0.3 mg/kg) as a rescue for patients developing new uveitis attacks on day 28 or later
Cantarini, 2012 [45]	Letter to the Editor	One woman, 20 years old BS (ISGC): 10-year history of recurrent oral and genital aphtosis, skin lesions, arthritis, abdominal pain and headache. Recurrent prolonged fever episodes. Mild to moderate non-specific mucosal inflammation and multiple ulcers in the ileocolic region. HLA-B51 positive	ANA (100 mg/day); interrupted for adverse reactions CAN (150 mg/8 weeks)
Ugurlu, 2012 [46]	Letter to the Editor	One girl, 16 years old BS Recurrent oral ulcers, erythema nodosum, eye disease and a positive pathergy test. Bilateral panuveitis and retinal vasculitis. Visual acuity 0.1 in the RE and 0.2 in the LE	ANA (2 mg/kg): ocular failure CAN (150 mg, single dose)
Bilginer, 2010 [47]	Case report	One girl Familial Mediterranean fever (FMF), BS (ISGC) Recurrent oral ulcers, skin lesions; positive pathergy test; secondary amyloidosis Highly reactive tuberculin test	ANA: 1 mg/kg, day Concomitant treatment: colchicine + isoniazid prohylaxis

Table 1 (continued)

First author, year, reference	Study design	Population; clinically relevant characteristics	Interventions and dosage
Botsios, 2008 [48]	Letter to the Editor	1 75 years old woman Severe refractory BS (ISGC) Recurrent fever, oral and genital ulcers, a positive pathergy test result, anemia, and elevated erythrocyte sedimentation rate and C- reactive protein level; HLA-B51 negative. Excision of distal colon (aphthous ulcers, coagulation necrosis, ischemic perforation, necrotizing lymphocytic venulitis, thrombosis, and serositis)	ANA (100 mg/day) Concomitant treatment: prednisone (5 mg/day) Reduced to 100 mg/every 2 days Re-started with 100 mg/day

ADA Adalimumab, *ANA* Anakinra, *AE* adverse event, *AZA* azathioprine, *BS* Behçet's syndrome, *BCVA* best corrected visual acuity, *BDCAF* Behçet's disease current activity form, *BDQOL* Behçet's disease quality of life, *BSAS* Behçet's syndrome activity score, *CAN* Canakinumab, *CCSss* corticosteroids, *DMARDs* disease modifying anti-rheumatic drugs, *ETDRS* early treatment diabetic retinopathy study, *FA* fluorescein angiography, *FMF* familial mediterranean fever, *GEV* gevokizumab, *HCQ* hydroxychloroquine, *IL* interleukin, *ICBD* International criteria for Behçet's disease, *ISGC* International study group criteria, *ISR* injection site reaction, *LE* left eye, *MRI* magnetic resonance imaging, *MTX* methotrexate, *NSAIDs* non-steroidal anti-inflammatory drugs, *OCT* optical coherence tomography, *RE* right eye, *SAA* serum amyloid A, *sAE* serious adverse event, *TNF* tumor necrosis factor, *VAS* visual analog scale

occurred in six out of 18 cases, and recovery was obtained in five of them following increase in IL-1 inhibitor dose ($n=4$) or introduction of DMARD co-treatment ($n=1$). In the retrospective cohort study by Emmi [60], 30 BS patients were treated with either ANA or CAN for different disease involvements. Complete response was achieved in all subjects with at least 12 months of follow-up (13/13), after a median time of 6 (± 2.2) and 3 (± 0.9) weeks for ANA and CAN, respectively. At 24 months, persistence to the initial treatment regimen was poor (overall cumulative survival of 26.3% and 40.6% for ANA and CAN, respectively), and a significant proportion of patients switched to other non-anti-IL1 treatment or from ANA to CAN. In another retrospective cohort study [59], treatment discontinuation during ANA or CAN therapy was reported in seven out of 18 subjects, due to inefficacy or loss of efficacy. In particular, three subjects switched to anti-TNF-α agents and four switched from ANA to CAN. The retrospective observational study by Fabiani [55] focused on the efficacy of ANA and CAN on subjects with refractory uveitis. Treatment with either ANA or CAN accounted for a significant reduction in the rate of ocular flares (from 200/100 patients/year to 48.8/100 patients/year; $p<0.0001$), in the proportion of subjects experiencing ocular flares (19/19 vs 6/19; $p<0.0001$), and in the percentage of eyes with vasculitis. Previous use of other biologics did not influence the response to ANA or CAN. Of note, the number of ocular flares was significantly higher in subjects with concomitant DMARDs treatment, while the best-corrected visual acuity (BCVA) was significantly higher in subjects with no DMARDs co-administration. Steroid dosage was significantly decreased at 12-month visit compared to baseline. ANA was interrupted in three out of 13 subjects for lack of efficacy and in one subject for loss of efficacy. CAN was interrupted in one out of six subjects for reactivation of BS at central nervous system level.

Efficacy of anakinra

Fifteen studies focused on the specific efficacy of ANA [39–49, 52, 54, 56, 58]. Among these, nine were letters to the editor, four were case reports or case series, one was an observational cohort study and one was a clinical trial.

Overall efficacy of anakinra

Efficacy of ANA 100 mg/day in inducing rapid clinical improvement and normalization of acute-phase reactants in adult population was reported by Emmi [40]. In another cohort study by Vitale [56], ANA was associated with complete and partial response in 15 and 19 out of 40 treated subjects. In a case series by Cantarini [43], of a mixed adult and pediatric population, ANA 100 mg/day or 2 mg/kg day induced complete BS resolution in seven out of nine

Table 2 Main results of the 24 included studies

First author, year, reference	Efficacy outcomes	Safety outcomes	Treatment persistency
Tugal-Tutkun, 2018 [50]	Ocular control Annual incidence rate of first ocular exacerbation: 52.7% versus 72.1%, for 24 and 21 patients-years at risk, respectively ($p > 0.05$) Mean change in BCVA score: -0.1 ± 12.2 letters vs -3.6 ± 13.8 letters ($p = 0.035$) Risk of BCVA worsening (≥ 10 letters): Odds Ratio 0.29, 95% CI 0.07 − 0.99, $p = 0.048$) Systemic response BDCAF changes: -0.3 ± 2.9 vs -0.9 ± 3.3 VAS changes: 6.0 ± 27.1 mm; median = 1.5 mm vs -6.1 ± 22.5 mm; median = − 1.0 mm	Patients with at least one AE: 92.7% vs 93.0% Most frequent AEs Visual blurring: 12.2% vs 0 Fatigue: 0 vs 14.0% Treatment-related infections: 2.4% vs 9.3% Emergent-positive interferon-gamma released assay: 4.9% vs 7.0% Drug hypersensitivity: 1 patients (4 events) vs 0 Drug-related AEs: 17.1% vs 18.6% Emergent SAEs: 31.7% vs 32.6%	–
Fabiani, 2018 [37]	Responders within 12 months ($n = 18$; Group 1); non-responders ($n = 18$; Group 2) Ocular involvement: 66.67% in Group 1 vs 16.7% in Group 2 ($p = 0.006$) Time to relapse: 79.7 ± 62.4 weeks in Group 1 vs 18.8 ± 14.2 weeks in Group 2 Recovery of efficacy: 5/6 in Group 1 (by adding methotrexate 15 mg/week to ANA in 1 case, or by increasing CAN dosage in 4 cases). In Group 2, dose adjustments did not allow any recovery of efficacy	Injection site-reactions ($n = 5$), anaphylaxis ($n = 1$), papillary carcinoma of urinary bladder ($n = 1$), recurrent urinary and high respiratory tract infections ($n = 1$)	At last follow-up: 11/18 in Group 1, mean period of 32.3 ± 14.7 weeks from the start Adverse events
Sota, 2018 [38]		89 safety events; 13 sAE. 2 deaths related to sAE 51 events during the first follow-up year and 38 events afterwards ($p < 0.0001$)	Treatment discontinuation owing to AE and sAE in 43 (8.2%) cases
Vitale, 2017 [52]	ANA: Complete disease control within a few days. During the following 18 months no BS manifestations. Steroid tapering. Stable neurological involvement. Bilateral uveitis reoccurred after 18 months CAN: No further ocular manifestations at the 6-month follow-up; additional gliotic lesions		Both discontinued
Orlando, 2017 [49]	ANA: good clinical results CAN: full control of symptoms. At a 36-month follow-up: complete control of disease activity and absence of neoplastic recurrence		ANA: discontinued for the onset of generalized urticarial rash related to ANA

Table 2 (continued)

First author, year, reference	Efficacy outcomes	Safety outcomes	Treatment persistency
Grayson, 2017 [54]	ANA 100 mg: Complete response: 2/6. Partial response: 2/6. Failure: 2/6 At month 12: Physician global VAS median 14 (range 3–30); Patient global VAS 35 (23–55); BDCAF 6 (3–7); BSAS 33 (15–57); BDQOL 14 (6–15) ANA 200 mg vs 100 mg: oral ulcers 65% vs 74% of days ($p=0.01$); genital ulcers 10% vs 22% of days ($p<0.01$). Dose escalation to 300 mg did not result in fewer oral or genital ulcers or milder ulcer severity	4 sAE in the same patient with ANA 100 and 200 mg (hospitalization to rule out thrombus, pulmonary arterial hypertension, pre-syncope, non-cardiac chest pain) Non-serious AEs: With ANA 100 mg: ISR (3), Oral thrush (1), Other (2). With ANA 200 mg: Upper respiratory infection (5), Alopecia (2), Oedema (2), Vaginal yeast infection (1), Other (9). With ANA 300 mg: Upper respiratory infection (2), Vaginal yeast infection (1), Other (2)	
Fabiani, 2017 [55]	1) Pre-treatment vs during the 12 months follow-up: ocular flares: 200/100 patients/year vs 48.8/100 patients/year ($p<0.0001$) 2) Co-administration of DMARDS vs monotherapy: ocular flares: 81.8/100 patients/year vs 0/100 patients/years ($p=0.03$). BCVA was significantly higher in subjects with no DMARDs co-administration (at baseline $p=0.007$; at 3 month $p=0.001$ and at 12 months $p=0.03$) 3) First-line biologic vs previous use of other biologics: $p=0.99$ 4) Steroid dosage significantly decreased at 12 months compared to baseline ($p=0.02$)	No AEs. ANA was interrupted in 3/13 subjects for lack of efficacy and in 1/13 subjects for loss of efficacy. CAN was interrupted in 1/6 subjects for reactivation of BS at central nervous system level	
Tugal-Tutkun, 2016 [51]	No significant worsening of non-ocular BS-related manifestations Main ophthalmologic parameters were markedly improved in all acute patients. No difference between the three dose regimens	No drug-related AEs; no allergic reactions AEs ($n=41$) in 18 patients sAEs ($n=6$) in 4 patients	17 patients withdrew due to ocular exacerbation ($n=11$), positive QuantiFERON TB test ($n=2$), non-response ($n=1$), non-medical reasons ($n=3$)
Vitale, 2016 [56]	ANA: in children: complete response: 0/1, partial response 1/1, failure 0/1. In adults: complete response: 15/40, partial response 19/40, failure 6/40 CAN: in children: complete response: 0/1, partial response 1/1, failure 0/1. In adults: complete response: 7/14, partial response 6/14, failure 1/14		
Emmi, 2017 [57]	Good clinical results in both patients rapidly	Well tolerated	Both patients maintained a daily subcutaneous injection of ANA (100 mg/day). No occurrence of new skin reactions during the 6 months of follow-up

Table 2 (continued)

First author, year, reference	Efficacy outcomes	Safety outcomes	Treatment persistency
Emmi, 2017 [58]	Rapid good clinical response At days 7: dramatic visual improvement and marked reduction of the optic nerve head swelling. During the 12 months follow-up: resolution of papillitis, increase of BCVA to 20/25, and absence of ocular inflammation during the following 12 months	No AEs or signs of tuberculosis reactivation	
Cantarini, 2017 [59]	7 patients stopped treatment because of inefficacy or loss of efficacy	No AE or sAE	7 patients stopped treatment
Emmi, 2016 [60]	12 months follow-up: 13/13 in complete remission; dose adjustment: 1/13; switch from ANA to CAN: 6/13 Median time of response: 6.0 (2.2) weeks for ANA and 3.0 (0.9) for CAN	AE in 4/27 with ANA (all were local cutaneous reactions), and 0 with CAN. No sAE	Overall cumulative survival at 24 months: 67.8%
Pagnini, 2015 [39]	19 months follow-up with ANA: Oral and skin ulceration, recurrent fever, arthralgia, headaches and abdominal pain were still present, associated with a persistent increase in inflammatory markers and mild anemia 4 months after switch to CAN: complete clinical and laboratory remission. Steroid treatment was gradually reduced to 5 mg/day 6 months follow-up: completely asymptomatic		Switch from ANA to CAN for inefficacy
Emmi, 2014 [40]	Case 1: rapid clinical improvement and normalization of acute-phase reactants; at 8 months of follow-up the patient maintains a good response Case 2: good control of eye symptoms, no flares during the 6-month follow-up	No sAEs	
Caso, 2014 [41]	Symptom-free during the first 6 months. Prednisone was tapered and NSAIDs interrupted. At 8 months: complete resolution of sacroiliac subchondral bone marrow oedema	No AEs	

Table 2 (continued)

First author, year, reference	Efficacy outcomes	Safety outcomes	Treatment persistency
Vitale, 2014 [42]	Case 1: ANA treatment: remarkable clinical improvement and normalization of SAA. CAN: prompt and complete response. At 12 months follow-up: symptom-free without evidence of disease relapse, with stable SAA concentration. After 16 months: deep vein thrombosis; CAN dosage was adjusted (every 6 weeks) Case 2: ANA treatment was ineffective. CAN, after 6 months follow-up: complete resolution. At 12 months follow-up: no disease relapse Case 3: ANA cleared ocular manifestations, no improvement of oral aphthosis and pseudofolliculitis. CAN: complete resolution, no clinical BS manifestations at 6-month follow-up	ANA: diffuse pruritic urticarial lesions ($n=2$) CAN: deep vein thrombosis ($n=1$)	Switch from ANA to CAN in all 3 cases (two for AEs, one for inefficacy)
Cantarini, 2015 [43]"	Resolution of disease activity: 7/9. Time to resolution: median of 2 weeks, range 1–4 Disease relapse: 7/7. Time to relapse, median: 18 weeks, range 9–72		
Emmi, 2013 [44]	Rapid and persistent disappearance of joint pain, mucocutaneous and bowel manifestations At 3 months: regression of ocular inflammation with complete clearing of the vitreous opacity and restoration of the retinal-blood barrier in both eyes. BCVA restored to 20/20 in both eyes		
Gül, 2012 [53]	Complete resolution of retinal findings was achieved in 4–21 days (median 14 days). Responses were durable, with a median duration of 49 days (range 21–97 days) Exacerbations: $n=5$ out of 7 (day 25–96)	2 AEs (a mild upper respiratory tract infection and a traffic accident) in 1 patient No drug-related AEs	All completed the 98-day study period
Cantarini, 2012 [45]	ANA: Remarkable clinical improvement and decrease in SAA concentration to normal values. CAN: Prompt and complete disease response. At 6 months: fever- and symptom-free, stable SAA concentrations	ANA: Diffuse pruritic urticarial lesions of increasing severity CAN: No AEs	ANA: Interrupted after 1 week
Ugurlu, 2012 [46]	ANA: continued eye attacks CAN: inflammation resolved and visual acuity improved. At 8 weeks: attack-free		

Table 2 (continued)

First author, year, reference	Efficacy outcomes	Safety outcomes	Treatment persistency
Bilginer, 2010 [47]	ANA: At 6 months follow-up: symptoms free; normalizations of albumin level and of acute-phase reactants. Relapse following ANA discontinuation Following reintroduction of ANA: excellent condition with normal acute-phase reactants, normal albumin levels, and stable levels of proteinuria At 18 months of follow-up: proteinuria gradually increased and albumin levels decreased. No FMF attacks and no mucosal or skin lesions		ANA discontinued at 6 months for shortage of supply
Botsios, 2008 [48]	After 10 days: Dramatic remission in fever, marked improvement in oral and genital ulcers, and in inflammatory markers After dose reduction: oral ulcers and fever reappeared Re-increase to daily dose: remission. After 20 months: disease-free		

ADA adalimumab, *ANA* anakinra, *AE* adverse event, *AZA* azathioprine, *BS* Behçet's syndrome, *BCVA* best corrected visual acuity, *BDCAF* Behçet's disease current activity form, *BDQOL* Behçet's disease quality of life, *BSAS* Behçet's syndrome activity score, *CAN* canakinumab, *CCSss* corticosteroids, *DMARDs* disease-modifying anti-rheumatic drugs, *ETDRS* early treatment diabetic retinopathy study, *FA* fluorescein angiography, *FMF* familial mediterranean fever, *GEV* gevokizumab, *HCQ* hydroxychloroquine, *IL* interleukin, *ICBD* international criteria for Behçet's disease, *ISGC* international study group criteria, *ISR* injection site reaction, *LE* left eye, *MRI* magnetic resonance imaging, *MTX* methotrexate, *NSAIDs* non-steroidal anti-inflammatory drugs, *OCT* optical coherence tomography, *RE* right eye, *SAA* serum amyloid A, *sAE* serious adverse event, *TNF* tumor necrosis factor, *VAS* visual analog scale

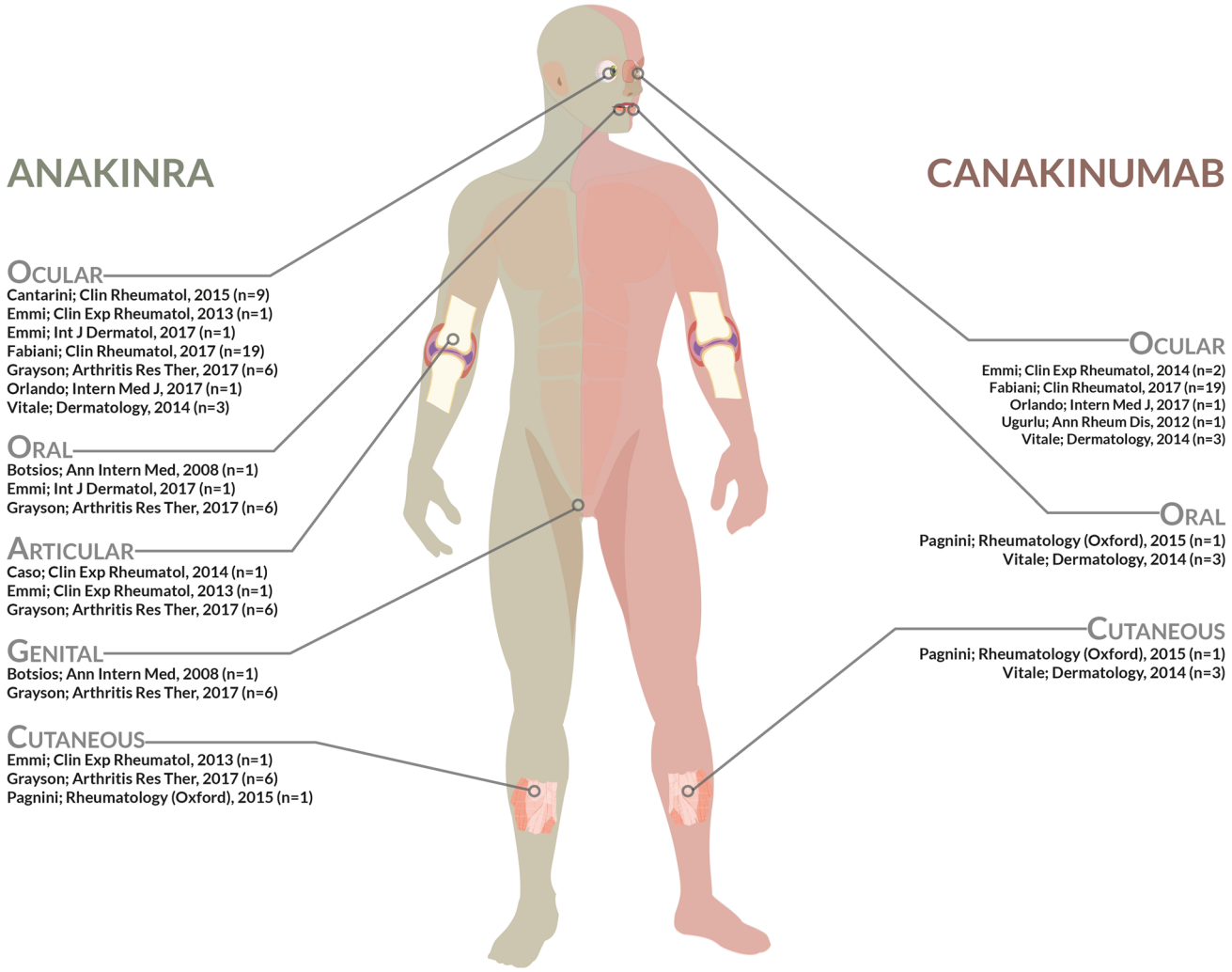

Fig. 2 Studies assessing the efficacy of anakinra and canakinumab in different Behçet's syndrome manifestations

subjects, after a median time of 2 weeks (range 1–4); nevertheless, relapse occurred in all seven subjects, after a median time of 18 weeks (range 9–72).

Efficacy for osteoarticular and mucocutaneous involvement

In a two-phase clinical trial by Grayson [54] on six adult BS subjects, complete and partial response to ANA 100 mg/day occurred in two subjects each. ANA was associated with improvement in joint pain (4/6), skin lesions (1/4), oral ulcers (5/6), and genital ulcers (2/2), and with no ocular inflammation. Compared to ANA 100 mg/day, ANA 200 mg/day accounted for higher proportion of improvement of oral and genital ulcers, as well as for milder severity of oral ulcers, but not of the genital ones. Dose escalation to ANA 300 mg/day did not result in fewer oral or genital ulcers or in milder ulcer severity. ANA 100 mg/day proved effective also in inducing complete resolution of sacroiliac subchondral bone marrow oedema in a man who failed previous DMARDs and infliximab (IFX) [41]. Also in a letter to the editor by Botsios [48], ANA 100 mg/day successfully controlled oral and genital ulcers and fever in a subject who failed previous treatments with DMARDs and IFX.

Efficacy for ocular manifestations

In a letter to the editor by Orlando [49], ANA was administered at the initial dose of 100 mg/day after ocular relapse following etanercept and IFX treatment, but an increase to 150 mg/day was required to obtain complete control of ocular manifestations. In a case reported by Emmi [44], a young woman suffering from bilateral retinal vasculitis and reduced visual acuity, was treated with ANA 100 mg/day after failure of adalimumab (ADA) and Rituximab. ANA 100 mg/day accounted for complete clearing of the vitreous opacity and restoration of the retinal-blood barrier in both eyes within

3 months from beginning of treatment, as well as for rapid and persistent disappearance of joint pain, mucocutaneous and bowel manifestations. Treatment with ANA 100 mg/day plus prednisone cleared ocular manifestations in a subject with monolateral panuveitis [42], but did not improve oral aphthosis and pseudofolliculitis. In another man with progressive worsening of vision associated with fever and recurrent oral ulcerations and with latent tuberculosis (TB), ANA 100 mg/day plus corticosteroids was associated with dramatic visual improvement and marked reduction of the optic nerve head swelling within the first weeks of treatment [58].

Efficacy for neuro-BS

In a letter to the editor by Vitale [52], use of ANA (100 mg/day) in a 30-year-old woman with neuro-BS and refractory ocular involvement was associated with complete disease control within few days from treatment beginning, headache disappearance, and stable neurological picture at magnetic resonance evaluation, while allowing steroid tapering. However, ANA was discontinued after 18 months due to reoccurrence of bilateral uveitis.

Efficacy for reduction of serum amyloid A (SAA) concentration

In the letter to the editor by Cantarini [45], ANA 100 mg/day provided remarkable decrease in serum amyloid A (SAA) concentrations to normal value in a young woman with a 10-year history of mucocutaneous and articular symptoms, abdominal pain, headache, and recurrent prolonged fever episodes. Normalization of SAA concentrations following ANA 100 mg/day treatment was reported also in a case report by Vitale [42].

Role of anakinra in children and adolescents

In a male child with BS since the age of 5, ineffectively controlled with DMARDs and intolerant to ADA treatment, the use of ANA at the initial dose of 2 mg/kg day, subsequently increased to 4 mg/kg day, was associated with poor disease control [39]. Unsuccessful ANA treatment was also reported in a letter by Ugurlu [46], in which ANA 2 mg/kg was associated with ocular failure. In the retrospective observational study by Vitale [56], use of ANA in one child was associated with partial response. On the other hand, ANA 1 mg/kg day was successfully used as first biologic treatment for secondary amyloidosis in a girl with FMF and BS, and high reactivity to tuberculin test [47].

Attempts of ANA discontinuation or reduction

Unsuccessful treatment discontinuation because of lack of supplies was reported by Bilginer [47]. Response was achieved again following treatment restart. In the study by Botsios [48], the attempt of reducing ANA dosage following disease remission was associated with the reoccurrence of ulcers and fevers, that disappeared after dose re-increase.

Efficacy of canakinumab

Efficacy of CAN as first-line IL-1 inhibitor was evaluated in two studies [40, 56]. In the case described by Emmi [40], CAN 150 mg/8 weeks was prescribed after failure of IFX and ADA treatment, and accounted for good control of eye symptoms and the absence of flares in the first 6 months of treatment. In the retrospective observational study by Vitale [56], use of CAN was associated with partial response in the treated child, and with seven and six complete and partial responses in the 14 adults treated with this drug.

Efficacy of canakinumab following anakinra treatment

Efficacy of CAN as second line IL-1 inhibitor following ANA discontinuation was evaluated in six studies [39, 42, 45, 46, 49, 52]. CAN (150 mg/8 weeks) proved effective in inducing complete remission and control of SAA levels in a young woman following ANA interruption for side effects [45]. Similarly, in three cases described by Vitale [42], CAN (150 mg/8weeks or 150 mg/6 weeks) accounted for complete response with no disease relapse after a follow-up of 6–12 months. In a letter to the editor by Orlando [49], CAN gave full control of ocular manifestations in a subject discontinuing ANA for adverse events, with complete ocular control at 36-month follow-up. In a letter to the editor by Vitale [52], CAN (150 mg every 4 weeks) was given to a 30-year-old woman with neuro-BS and refractory ocular involvement, following ANA ocular failure. In this patient, CAN accounted for good ocular efficacy, but was discontinued because of poor control of the neurologic involvement.

Role of canakinumab in children and adolescents

CAN (4 mg/kg every 28 days) was effectively used in a 9-year-old boy who failed previous ANA treatment. Within 4 months from CAN beginning, complete clinical and laboratory remission was obtained, and steroid was gradually tapered; the boy remained completely asymptomatic during a 6-month follow-up [39]. In the case letter by Ugurlu [46], a 16-year-old girl with ocular failure unsuccessfully treated with DMARDs, IFX, ADA, and ANA, had successful resolution of eye inflammation and improvement of visual acuity following treatment with CAN 150 mg in a single dose.

Efficacy of gevokizumab

Use of GEV in BS was evaluated in three clinical studies [50, 51, 53], all conducted on patients with ocular involvement. In a first non-controlled pilot study on seven BS patients with acute posterior or panuveitis and/or retinal vasculitis, a single intravenous infusion of GEV 0.3 mg/kg was associated with complete resolution of retinal involvements within 4–21 days, and with improvement in visual acuity in five patients [53].However, exacerbations occurred in five cases, and four patients needed a second GEV infusion.

In a prospective, open-label, randomized, parallel-group phase 2 trial conducted on 21 patients with acute uveitis or at risk of exacerbations, GEV was initially administered intravenously at the dose of 30 or 60 mg, and was then administered at the dose of 30 mg subcutaneously or 60 mg subcutaneously or 30 mg intravenously every 4 weeks. GEV was discontinued in 17 patients, mainly because of ocular exacerbations ($n=11$). In the remaining 14 patients with acute uveitis, response was achieved within 21 days in all cases and main ophthalmologic parameters significantly improved, with no difference between the three dose regimens.

In an international, randomized, double-blinded phase III study [50], 83 BS patients with uveitis involving the posterior segment were randomized to GEV 60 mg every 4 weeks or placebo. Results failed to demonstrate a superiority of GEV as compared to placebo in controlling the number and the timing of ocular exacerbations, although GEV was associated with a significantly lower decrease in BCVA score.

Safety profile

Occurrence of adverse events during ANA or CAN treatment was reported in eight studies [37, 38, 42, 45, 49, 54, 57, 60].

In a case–control study by Fabiani [37], most common adverse events reported during ANA or CAN treatment were injection site-reactions (ISR; five cases out of 36 patients), whereas anaphylaxis, papillary carcinoma of urinary bladder, recurrent urinary and high respiratory tract infections occurred in one patient each. In an observational study by Emmi [60], use of ANA was associated with local cutaneous reactions in four out of 27 cases, whereas use of CAN in three subjects for a 24-month follow-up was not associated with any side effect. In the two-phase clinical trial by Grayson [54] conducted on six subjects, one patient was diagnosed with pulmonary arterial hypertension during the trial, however, onset was suspected prior to enrolment. No relationship was found between the frequency of adverse events and the dose of ANA. Discontinuation of ANA treatment due to adverse events was reported by Cantarini [45], Vitale [42], and Orlando [49]. In Cantarini [45], ANA was associated with pruritic urticarial lesions of increasing severity. In the two cases described by Vitale [42], ANA was associated with diffuse pruritic urticarial lesions. In the case described by Orlando [49], ANA was discontinued following the onset of generalized urticarial rash.

As for CAN, in the case described by Vitale [42], deep venous thrombosis occurred 16 months after the beginning of CAN treatment, and needed dose adjustment. In a recent observational study by Sota [38], the safety profile of ANA and CAN was evaluated in 475 subjects with BS or with other immune-mediated pathologies requiring IL-1 inhibition. 89 adverse events were recorded; of them, 13 (14.61%) were serious and 2 led to death. Treatment duration was the only variable inversely associated with the risk of adverse events. Age, concomitant DMARDs treatment, gender, previous biologic treatment, and posologic regimen did not influence the occurrence of adverse events or serious adverse events. Drug retention rate was significantly influenced by the occurrence of adverse events, particularly for ANA.

GEV was associated with a good safety profile and poor drug-related adverse events. In the pilot study by Gül et al., [53], out of seven treated patients, only one patient experienced two (drug-unrelated) adverse events, namely mild upper respiratory tract infection and a traffic accident. Similarly, in the phase II trial by Tugal-Tutkun [51], no drug-related adverse events and no allergic reactions were reported, while drug-unrelated adverse events and serious drug-unrelated adverse events occurred in 18 and 4 out of 21 patients, respectively. In the randomized, placebo-controlled phase III trial by Tugal-Tutkun [50], adverse events and serious adverse events involved 92.7% and 31.7% of patients, respectively, although similar proportions were found in the placebo group. Specifically, drug-related AEs involved 17.1% vs 18.6% of patients in the GEV vs placebo group, and most frequent AEs included BS-related manifestations, visual blurring, fatigue, and arthralgia. Treatment-related infections were detected in 2.4% of patients treated with GEV.

Desensitisation

Successful desensitisation to previous ANA treatment interrupted for severe delayed ISR, was described in two subjects. The 4-day procedure was well tolerated and allowed a successful reintroduction of ANA (100 mg/day) during a 6-month follow-up [57].

Discussion

BS is a disease of unknown etiology characterized by clusters of heterogeneous symptoms. Mucocutaneous lesions represent the hallmark of BS [61, 62]. Despite BS was originally considered a dermatological disease, morbidity and

mortality for BS are mainly related to ocular, major vascular and neurological involvements [63]. Thus, BS might indeed not be a single nosological entity, but rather a complex syndrome with different phenotypes [64].

It is well described in BS literature that single drugs account for different organ responses [13, 24, 25, 64–67], suggesting that therapeutic approach to BS should be tailored to the specific patients' manifestations, rather than the presence of BS per se.

Evidence from the present systematic review suggests that IL-1 inhibitors may represent an effective therapeutic option in limited clusters of BS involvement. Specifically, treatment of either ANA (100 mg/day or 200 mg/day) or CAN (150 mg/8 weeks or 150 mg/6 weeks) could be effectively used to control mucocutaneous symptoms. In particular, ANA 200 mg/day has been associated with a better control of oral and genital ulcers as compared to ANA 100 mg/day. Nevertheless, evidence on the efficacy of ANA and CAN in controlling mucocutaneous symptoms comes from a limited number of observed patients [42, 48, 54].

Results from this systematic review also suggest that ANA 100 mg/day is good for osteoarticular manifestations, although this evidence comes from a clinical trial with a limited number of patients [54] and a single case report [41].

ANA 100 mg/day (eventually increased to ANA 150 mg/day) and CAN represent an effective and safe therapeutic option for BS-related uveitis, with evidence suggesting a significant reduction of the rate of ocular inflammatory flares, the resolution of active retinal vasculitis, the preservation of visual acuity, and the significant decrease of steroid dosages. Evidence of the effective use of ANA and CAN to control ocular manifestations is supported by data from a high-quality cohort study on 19 subjects [55] and from a case–control study on 36 subjects [37]. In addition, specific evidence on ANA is supported by two letters to the editor and two case reports [42, 44, 49, 58], whereas specific evidence on CAN comes only from a letter to the editor [49]. On the other hand, use of GEV for the control of ocular BS involvements is controversial, as current trials provided unclear evidence on its efficacy [50, 51, 53].

Notably, findings from an observational study [55] and a case report [39] suggest a possible contribution of anti-IL-1 treatments in steroid sparing, although further evidence is needed.

Interestingly, some evidence suggests a possible role of both ANA 100 mg/day and CAN 150 mg/8 weeks in normalizing SAA levels and preventing secondary amyloidosis in subjects with increased SAA concentration. However, given that this evidence is based only on two letters to the editor [42, 45], the real benefits of IL-1 inhibitors for the SAA control should be further investigated in details.

As for the use of anti-IL-1 treatments in the pediatric population, discrepant evidence was found; particularly, CAN might represent an effective treatment in this population subset, although further investigation is needed [39, 46].

Based on the results of this systematic review, current evidence does not support the use of ANA or CAN for the general management of BS, i.e., for the treatment of BS manifestations other than ocular, mucocutaneous, and articular.

Notably, findings from this review do not support ANA discontinuation or dose reduction following achievement of BS control.

Of particular relevance, findings from included studies suggest a poor persistence to anti-IL-1 treatment, with consistent percentages of switch between anti-IL-1 inhibitors or to different immunosuppressive treatments, due to inefficacy or side effects [37–39, 42, 47, 49, 59, 60].

During anti-IL-1 treatment, most frequent side effects are local or diffuse cutaneous reactions and ISR. Based on current evidence, such safety concerns are more relevant in patients treated with ANA. Given that occurrence of side effects appeared as unrelated to patients' age, gender, concomitant DMARDs treatment, previous biologic treatment, and posologic regimen, these factors cannot be considered as determinants for the choice or the avoidance of anti-IL-1 treatment. In patients effectively treated with ANA who develop severe delayed ISR to this drug, desensitisation protocols can be applied with successful restart of ANA treatment [57]. In patients that need ANA discontinuation due to treatment failure or adverse events, results from this systematic review further suggest that CAN could be effectively used to control BS. This finding is supported by four letters to the editor and one case report [39, 42, 45, 46, 49].

This study represents the first systematic review evaluating the efficacy and safety of ANA, CAN, and GEV in different BS manifestations, and is strengthened by the fact that both randomized trials and observational studies have been included.

Of course, this review has some limitations. First, more than half of included studies were letters to the editor, case reports or case series. Second, the baseline clinical characteristics and disease manifestations of subjects varied among included studies. Finally, since BS is typically characterized by intermittent phases of spontaneous remissions and exacerbations, the true effect of the treatment cannot be easily defined, particularly in uncontrolled studies.

Current evidence suggests that the choice of the most appropriate pharmacological treatment of BS should be evaluated in relation to different disease manifestations [43, 60]. Over the past decade, new therapeutic options have become available for treatment of BS, such as cytokine blocking agents, and in particular anti-IL-1 agents. Since evidence on these treatments mainly derives from limited local experiences, the results from this systematic review suggest the potential benefits of the use of IL-1 inhibitors in specific BS involvements such as ocular, mucocutaneous, and articular

manifestations. The possible contribution of IL-1 inhibitors in reducing SAA levels, as well as their efficacy in the pediatric population should be further investigated. On the other hand, use of IL-1 inhibitors in general BS involvements (especially as first-line treatment) is not yet clearly supported by literature.

Acknowledgements The authors wish to thank Stefano Salvati and Javier Hernández Plasencia for their help in preparing the Fig. 2.

Author contributions All authors contributed to the conception of the work. Authors AB and GE contributed to the design of the work and in the acquisition and analysis of data. Authors ES, GDS, GL, CS, LC, AS, and GE contributed in the interpretation of data for the work. Authors AB and GE contributed in drafting the work, and all other authors revised it critically for important intellectual content. All authors approved the final version of the manuscript to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest LC received research grant and participated at speaker's bureau by Sobi and Novartis. GE received fee from SOBI for consultancy and participated at speaker's bureau by Novartis. AS received fee from SOBI for consultancy. All other authors declare that they have no conflict of interest.

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