REVIEW

Biologic Therapies and Small Molecules for the Management of Non-Infectious Scleritis: A Narrative Review

Jurgen Sota · Matteo-Maria Girolamo · Bruno Frediani ·

Gian Marco Tosi · Luca Cantarini (iD) · Claudia Fabiani

ABSTRACT

Scleritis refers to a wide spectrum of ocular conditions ranging from mild to sight-threatening scleral inflammation that may compromise visual function and threaten the anatomical integrity of the ocular globe. Most aggressive forms like necrotizing or posterior scleritis are often difficult-to-treat cases, refractory to conventional treatment. The association with systemic diseases, namely rheumatoid arthritis, Sjögren syndrome, granulomatosis with polyangiitis, and relapsing polychondritis, may have prognostic implications as well. A better understanding of the pathogenesis of ocular inflammatory diseases have paved the way to more effective and targeted treatment approaches. In this regard, a growing body of evidence supports the potential role of biologic agents in the management of non-infectious scleral inflammation, either idiopathic or in a background of immune-mediated systemic disorders. Biologic agents such as anti-tumor necrosis factor agents, interleukin-1 and interleukin-6 inhibitors as well as CD20 blockade have displayed promising results. More specifically, several studies have reported their ability to control scleral inflammation, reduce the overall scleritis relapses, and allow a glucocorticoid-sparing effect while being generally well tolerated. Anecdotal reports have also been described with other biologic agents including abatacept, ustekinumab, daclizumab, and alemtuzumab as well as targeted small molecules such as tofacitinib. Further studies are warranted to fully elucidate the role of biologic agents in non-infectious scleritis and investigate specific areas with the aim to administer treatments in the context of personalized medicine. This review summarizes the available data regarding clinical trials, small pilot studies, and real-life experience of the last two decades reporting the use of biologic agents in the management of non-infectious scleritis.

Keywords: Scleritis; Biologic agents; Anti-tumor necrosis factor; Rituximab; Interleukin-1 inhibitors; Tocilizumab

J. Sota · B. Frediani · L. Cantarini (✉)
Rheumatology Unit, Department of Medical Sciences, Surgery and Neurosciences, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinics, University of Siena, Policlinico "Le Scotte", viale Bracci 16, 53100 Siena, Italy
e-mail: cantariniluca@hotmail.com

M.-M. Girolamo · G. M. Tosi · C. Fabiani
Ophthalmology Unit, Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

Key Summary Points

This review summarizes the available evidence regarding the management of refractory non-infectious scleritis with biologic agents.

Non-infectious scleritis, particularly in its most aggressive forms such as necrotizing scleritis and posterior scleritis, may lead to visual impairment and severe sight-threatening ocular sequelae.

Monoclonal antibodies targeting tumor necrosis factor alpha, interleukin-6, CD20, and anti-interleukin-1 agents represent reliable options.

Biologic agents have shown to control scleral inflammation, reduce the overall scleritis relapses, and allow a glucocorticoid-sparing effect.

Management of scleritis must take place in a multidisciplinary setting in order to maximize treatment benefits while minimizing safety concerns.

INTRODUCTION

The term scleritis includes a wide spectrum of clinical entities characterized by inflammation of the sclera. This clinical condition, particularly in its most aggressive forms such as necrotizing scleritis and posterior scleritis, may lead to visual impairment and severe sight-threatening ocular sequelae. Indeed, permanent scarring of the adjacent inflamed ocular structures may compromise visual function and result in anatomical damage as well. Severe and untreated cases may lead to perforation, which is among the most feared complications since it may be responsible for eye loss [1]. The overarching principles of its treatment consist in controlling the ocular inflammation and inducing long-term remission, thus preventing further sight-threatening complications and

structural irreversible ocular impairment. Oral glucocorticoids (GCs) remain the mainstay of the short-term management of scleritis, while pulse intravenous steroids are reserved in sight-threatening emergencies requiring a rapid control of inflammation [2, 3]. Subconjunctival GC injections may be used as an adjunct therapy to systemic GCs to control acute exacerbation of unilateral non-infectious non-necrotizing scleral inflammation [4]. In recalcitrant and most aggressive cases of non-infectious scleritis, several biologic agents have been used to suppress ocular inflammation and reduce the burden of systemic GCs [5–11]. Despite the revolution brought by biologic agents in many medical specialties, only an exiguous number of clinical trials, retrospective case series, or isolated case reports have been reported in literature regarding their employment in the treatment of non-infectious scleritis. Therefore, treatment guidelines or specific management protocols that include systemic immunosuppressive drugs are currently not available because of the lack of evidence-based data. We reviewed the current literature regarding the efficacy and safety of biologic agents in refractory non-infectious scleritis, with the aim to summarize the real-life experience in the management of this sight-threatening condition.

RESEARCH STRATEGY

A comprehensive literature research via Pubmed was performed and included articles published from June 2001 to June 2021. The following terms were searched in Medical Subjects Headings and/or as entrée words: "scleritis" and "biologic agents". Thereafter, the name of each drug deemed relevant to the management of scleritis was searched together with the word "scleritis". In particular, the following items were employed: "tumor necrosis factor inhibitors", "adalimumab", "infliximab", "etanercept", "golimumab", "certolizumab", "rituximab", "ofatumumab", "ocrelizumab", "anakinra", "canakinumab", "tocilizumab", "sarilumab", "siltuximab", "sirukumab", "olokizumab", "clazakizumab", "abatacept", "ustekinumab", "secukinumab", "ixekizumab",

"daclizumab", "alemtuzumab", "interferon", "interferons" "baricitinib", "tofacitinib", "filgotinib", and "upadacitinib", each combined with "scleritis". Case series, observational studies, and clinical trials were reviewed to find eligible papers according to the goal of our manuscript. Subsequently, relevant references cited in the eligible papers were searched by hand. This article is based on previously conducted studies and does not contain any new study with human participants or animals performed by any of the authors.

TUMOR NECROSIS FACTOR INHIBITORS

Adalimumab

The first case reports and small case series of non-infectious scleritis successfully treated with adalimumab (ADA) [12–16] were followed by retrospective studies assessing its efficacy in larger samples of refractory patients [7, 11, 17–19]. Ragam et al. conducted a retrospective chart review of 17 patients with non-infectious, non-necrotizing scleritis and found that monoclonal anti-tumor necrosis factor alpha (TNFα) were able to reduce scleral inflammation and to concomitantly reduce the use of systemic GCs. More specifically, 10 patients were initially treated with infliximab (IFX) and seven with ADA. Control of active inflammation for at least 2 months was achieved in 15 out of 17 patients. The total rate of inflammatory control on ADA which included seven patients on first trial and two patients after IFX failure was 67% [7]. Moderate control of inflammation and a GC-sparing effect were also observed in nine patients with scleritis in a study investigating ADA efficacy. Almost half of the eyes achieved control of inflammation during follow-up. In addition, cystoid macular edema resolved in the majority of cases [17]. In their real-world prospective analysis, Sharma et al. found TNFα inhibitors ADA and IFX to be successful in several ocular inflammatory diseases. A sustained remission was noted in 91% of the cases, of whom four were diagnosed with non-infectious scleritis. Further detailed data on

scleritis were not provided. These findings supports the long-term efficacy of TNF inhibitors and their GC-sparing effect [18]. We recently reported 19 patients diagnosed with non-infectious scleritis and treated with monoclonal TNFα blockers, mainly ADA (n = 13), followed by IFX (n = 5) and golimumab (GOL) (n = 1). Monoclonal TNFα inhibitors were shown to significantly reduce relapses as well as to control scleral inflammation both rapidly and with a long-lasting effect. Moreover, they allowed a GC-sparing effect and were associated with a good safety profile [11]. Successful results with TNFα inhibitors have also been reported in three patients affected by relapsing polychondritis (RP) [20]. Table 1 shows the retrieved studies regarding TNF inhibitors employed in the management of non-infectious scleritis and some of their respective findings.

Infliximab

Similarly to ADA, IFX may be considered as a viable option in patients with refractory scleritis. The only prospective evidence regarding IFX employment in non-infectious scleritis dates back to 2009. In this prospective open-label pilot study, all patients met the primary outcome by achieving quiescence of their active scleritis by week 14 without associated conventional immunosuppressants. Additionally, four out of five patients achieved a sustained quiescence on treatment and 60% were able to successfully taper prednisone to daily doses lower than 10 mg [21]. These promising data were further corroborated by real-world experience in relatively large samples of non-infectious scleritis. Sobrin and colleagues found IFX therapy to be effective for the treatment of refractory ocular inflammation, with a low incidence of adverse events (AEs) prompting discontinuation. Nine out of 10 patient were classified as responders and one as a partial responder requiring alkylating agent therapy. Five patients were able to reduce their concurrent immunosuppressive therapy and three patients with scleritis were able to remain relapse-free despite having discontinued all medications [22]. Almost identical results were reported by

Table 1 Anti-tumor necrosis factor therapy in the treatment of non-infectious scleritis

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Sadhu, 2020 [19]	CS	ADA	3	Diffuse AS (n = 1) NAS (n = 2)	RA (n = 1) Idiopathic (n = 2)	Clinical response, GC-sparing effect	NR	18.5
Khalili, 2020 [41]	CR	IFX	1	PS + anterior uveitis	Idiopathic	Successful control of inflammation. Improvement in visual acuity. Remission on 4 years. Mild relapse 6 months after IFX cessation responsive to ibuprofen 400 mg 3 times daily	NR	60 on IFX. 108 in total
Fabiani, 2020 [11]	RS	ADA (n = 13) IFX (n = 5) GOL (n = 1)	19	AS	RA (n = 5), PsA (n = 4), BS (n = 3), idiopathic (n = 3), CD (n = 1), SpA (n = 1), RP (n = 1), Takayasu arteritis (n = 1)	Significant reduction in scleritis grading and ocular relapses. Significant GC-sparing effect and stable BCVA. Good drug retention rate (almost 60% at 12-month follow-up and an estimated 52% at 36-month follow-up)	Severe urticaria (n = 1), pneumonia and paradoxical psoriasis (n = 1)	18
Amer, 2020 [50]	CR	GOL	1	Necrotizing PS	PsA	No disease progression or evidence of association AU or PU or CME	NR	72 (24 on GOL)

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Iwahashi, 2019 [24]	CS	IFX	2	AS (n = 1) AS + PS (n = 1)	RA	Clinical improvement. Treatment discontinuation due to paradoxical ocular AE One patient switched to tocilizumab with complete resolution of scleritis and macular edema	Macular edema and vitreous opacity (n = 1) Exacerbation of PS, dense vitritis and serous retinal detachment (n = 1)	4.5
Dutta Majumder, 2019 [51]	CR	GOL	1	NAS	Idiopathic	Proper control of scleritis allowing the insertion of Ahmed glaucoma valve	NR	–
Durrani, 2017 [17]	RS	ADA	9	NS scleritis	NR	Resolution of inflammation in 47% of the eyes with recalcitrant disease and treated with multiple immunosuppressants. GC-sparing effect Cystoid macular edema resolved in 3/4 eyes Discontinuation in 4 patients due to ineffectiveness	Skin reaction (n = 1), rash (n = 1), fatigue and body ache (n = 1), angina (n = 1), swelling of rectus muscles (n = 1), retinal detachment (n = 1)	31.2

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Lawuyi, 2016 [16]	CS	ADA	2	NAS (n = 2)	RA (n = 1) Idiopathic (n = 1)	Clinical resolution and control of scleral necrosis	Gastroenteritis (n = 1), herpes zoster reactivation (n = 1)	7.5
Sainz-de-la-Maza, 2016 [20]	CS	IFX (n = 5) ADA (n = 5) CZP (n = 1) ETN (n = 1)	13	Diffuse AS (n = 10) NAS (n = 3)	RP	IFX and ADA were effective in 1 and 2 patients, respectively. Two patients developed scleritis after IFX therapy and 1 of them was administered ADA and ETN without success. Finally CZP pegol was given, with no further relapses of scleritis	2 paradoxical scleritis reactions under IFX	21
Akhtar, 2015 [15]	CR	ADA	1	AS	Takayasu arteritis	Marked improvement of scleritis, GC-sparing effect	NR	18

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Ragam, 2014 [7]	RS	ADA (n = 7)IFX (n = 10)	17	Non-necrotizing scleritis	RA (n = 12) RA + CD (n = 2) RA + GD (n = 1) GD (n = 1) CD (n = 1)	Control of active inflammation for at least 2 months was achieved in 88% of patients. Five (29%) patients ended up switching from one TNFα inhibitor to another. Stable visual acuity. No significant differences between ADA and IFX	Allergic reaction to a single infusion of IFX (n = 1). Transaminitis on ADA treatment (n = 1)	25.8
Hata, 2012 [40]	CR	IFX	1	Nodular scleritis with superficial punctate keratitis	RA	Scleritis and infiltrative keratitis completely improved. No reoccurrence of ocular disease	No side effects	NR
Sassa, 2012 [48]	CR	ETN	1	NS scleritis	RA	Development of scleritis 1 month after ETN reintroduction and reoccurrence during rechallenge. Clinical resolution upon switch to IFX	Paradoxical scleritis after ETN therapy	100 on ETN, 12 on IFX

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Gaujoux-Viala, 2012 [47]	CS	ETN	3	AS with uveitis (n = 2) NAS (n = 1)	RA	Rapid remission after ETN discontinuation. One patient experienced a dechallenge-rechallenge phenomenon	Paradoxical scleritis after ETN therapy	25.7
Tlucek, 2020 [52]	CR	CZP pegol	1	NS scleritis	RA	Resolution both symptomatically and on ophthalmological examination	NR	5
Bawazeer, 2011 [14]	CR	ADA	1	Nodular AS	Idiopathic	Rapid control of scleritis within 3 months after failure of IFX, GC-sparing effect	No side effects	60 (24 on ADA)
Oh, 2011 [39]	CR	IFX	1	AS + PS + PUK	Juvenile RA	After the third IFX infusion, the corneal ulceration stopped, and conjunctival hyperemia and ocular discomfort were relieved. Systemic immunosuppression tapered after 3 months	NR	12

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Doctor, 2010 [5]	CS/RS	IFX	10	Diffuse AS (n = 4), Nodular AS (n = 3), Sclerouveitis (n = 3), CME (n = 1), PUK (n = 1), interstitial keratitis (n = 1), anterior uveitis (n = 1)	Idiopathic (n = 3), RA (n = 2), CD (n = 2), RA + CD (n = 2), BS (n = 1)	Favorable response in 90% of the patients, with 6 of them achieving remission and cessation of concomitant immunosuppression. Monthly infusions may be required to maintain remission	Drug-induced lupus (n = 1), Streptococcal upper respiratory infections (n = 2), Herpes zoster (n = 1)	16.8
Restrepo, 2010 [13]	CR	ADA	1	Nodular AS	RA	Control of ocular and extraocular manifestations at 3-month follow-up		6
Jabbarvand, 2010 [38]	CR	IFX	1	NAS + PUK	RP	Complete remission	NR	12
Kontkanen, 2010 [37]	CR	IFX	1	NSA	GPA	Rapid clinical response. Improvement in visual acuity	NR	24
Abalos Medina, 2010 [36]	CS	IFX	1	NAS	RA	Rapid clinical improvement, resolution of symptoms after the 3rd IFX infusion	NR	4
Herrera-Esparza, 2009 [35]	CR	IFX	1	AS	RA	Clinical improvement 2 weeks following the first IFX infusion	No side effects	24

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Sen, 2009 [21]	CT	IFX	5	AS	HLA-B27 scleritis (n = 1) GPA (n = 1) Cogan's syndrome (n = 1) Idiopathic (n = 1)	All patients achieved control of active scleritis within 14 weeks. One patient with GPA developed new-onset intraocular inflammation after 14 weeks. Clinical resolution in 4 out of 5	Ear infection with transient decreased hearing, UTI, lower RTI, and facial rash (n = 1) UTI, diarrhea, upper RTI, nasal congestion and headache, mouth sores, head tremor, occasional numbness and tingling in extremities (n = 1)	10.8
Ahn, 2009 [26]	CS	IFX	3	NAS	Idiopathic	Clinical resolution, choroidal and retinal detachment subsided	No complication observed	16
Lopez-Gonzalez, 2009 [34]	CS	IFX	1	Necrotizing scleritis	Idiopathic	Clinical response. Inactivity of posterior pole. GC-sparing effect. Preserved visual acuity	No AE	2.5
Le Garrec, 2009 [46]	CS	ETN	2	Nodular AS	RA	Development of nodular AS in 2 patients, 17 months and 12 months after ETN initiation, respectively	Paradoxical nodular AS (n = 2)	14.5
Huynh, 2008 [12]	CS	ADA (n = 2), IFX (n = 1)	3	NS scleritis	RA (n = 1) Psoriasis (n = 3)	Clinical response, reduction in inflammatory grade	No significant clinical or laboratory AE	8.5

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Culver, 2008 [33]	CR	IFX	1	PS + orbital miositis	CD	IFX had a partial efficacy on ocular disease and no impact on intestinal symptoms. Two months after cyclophosphamide infusions the patient had a recurrence and was treated with ADA with no further relapses	NR	Roughly 10
Morley, 2008 [32]	CS	IFX	1	NAS	Surgically induced necrotizing scleritis	IFX discontinuation after the 3rd infusion due to general malaise. Lesion resolved 1 month after IFX cessation	General malaise after 3rd infusion	2.5
Weiss, 2007 [31]	CR	IFX	1	PS + papillitis	Idiopathic	Clinical relief in 10 days following the first IFX infusion. Reduction of scleral swelling on B-mode ultrasound examination and regression of papillitis at fundoscopy. Complete remission at 4 months	No side effects	16

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Sobrin, 2007 [22]	RS	IFX	10	NS scleritis (n = 6) Nodular scleritis (n = 2) Scleritis + anterior uveitis (n = 1) Scleritis + panuveitis (n = 1)	RA (n = 2) CD (n = 1) RP (n = 1) Reactive arthritis (n = 1) Ankylosing spondylitis (n = 1) Idiopathic (n = 4)	Nine out of 10 patient were classified as responders and 1 as partial responder requiring alkylating agent therapy. Five patients were able to reduce their concurrent immunosuppressive therapy. Three patients were able to remain relapse-free while not taking any medication	Lupus-like reaction causing treatment withdrawal (n = 1)	20
Archia, 2006 [30]	CR	IFX	1	NAS + PUK	RA	Dramatic improvement after the first IFX infusion	NR	5
Galor, 2006 [44]	RS	22 patients with uveitis and scleritis IFX (n = 13) ETN (n = 9)	4	AS (n = 3) NAS (n = 1)	RA (n = 2) RP (n = 2)	Two patients developed their first episode of anterior scleritis 8 and 31 months after ETN treatment	Paradoxical AS (n = 1) and NAS (n = 1) after ETN treatment	–
El-Shabrawi, 2005 [29]	CR	IFX	1	NAS + PUK, anterior uveitis	GPA	Clinical improvement, drug-sparing effect, visual acuity improvement	Acute herpes zoster infection	13

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Ashok, 2005 [23]	CR	IFX	1	NAS + PUK	RA	Dramatic response after three infusions of IFX. Improvement of visual acuity. Relapse upon reduction of prednisolone at 12.5 mg daily. Clinical resolution after increased dosages from 3 mg/kg to 5 mg/kg of IFX	NR	24
Cazabon, 2005 [28]	CR	IFX	1	Diffuse AS	RP	Clinical resolution of ocular and systemic manifestations	No AE reported	6
Díaz-Valle, 2004 [27]	CR	IFX	1	Diffuse AS	RA	Clinical improvement after the 2nd infusion of IFX. Resolution after 3rd infusion	NR	6
Murphy, 2004 [25]	CS	IFX	4	NS scleritis (n = 3) NAS + PUK (n = 1)	RA (n = 1) pANCA renal vasculitis (n = 1) Idiopathic (n = 2)	Three out of 4 patients achieved remission. One patient showed a partial response but treatment was withdrawn. Repeated infusions were required to maintain remission	Infusion-related reaction	10.5

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Hernandez-Illas, 2004 [42]	RS	ETN	10	Diffuse AS ($n = 3$) NeS ($n = 3$) Sectoral diffuse scleritis ($n = 1$) PUK ($n = 1$) Recurrent corneoscleral ulcerations ($n = 1$) Peripheral necrotizing corneal ulcerations ($n = 1$)	RA (n = 3), GPA ($n = 2$), PsA ($n = 1$), CD ($n = 1$), RP ($n = 1$), idiopathic ($n = 1$), arthritis ($n = 1$)	ETN proved to be effective in resolving scleritis and sterile corneal ulcerations by controlling inflammation, arresting tissue ulceration, and permitting in many cases tapering or cessation of immunosuppressive therapies	No infections or systemic toxicities observed	–
Tiliakos, 2003 [45]	CS	ETN	1	NS scleritis	RA and Sjögren's syndrome	Development of scleritis 18 months after ETN treatment, treated with local and systemic GC, local cyclosporine and azathioprine. ETN was continued during disease course	Paradoxical scleritis after ETN therapy	36

Table 1 continued

First author, year reference	Study design	Biologic agent	N°	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Smith, 2001 [43]	RS	ETN	6	NS scleritis	RA	Scleritis developed in 3 patients under ETN therapy, 1, 2, and 6 months respectively. In the remaining 3 patients, ocular disease was not influenced by TNF blockade ($n = 1$), remained quiescent ($n = 1$), or was minimally active ($n = 1$),	Paradoxical scleritis ($n = 3$)	–

ADA adalimumab, *AE* adverse event, *AS* anterior scleritis, *AU* anterior uveitis, *BCVA* best corrected visual acuity, *BS* Behçet's syndrome, *CD* Crohn's disease, *CME* cytoid macular edema, *CR* case report, *CS* case series, *CT* clinical trial, *CZP* certolizumab, *ETN* etanercept, *GC* glucocorticoid, *GD* Grave's disease, *GPA* granulomatosis with polyangitis, *GOL* golimumab, *IFX* infliximab, *N°* number of patients with scleritis, *NAS* necrotizing anterior scleritis, *NeS* necrotizing scleritis, *NR* not reported, *pANCA* perinuclear antineutrophil cytoplasmic antibody, *PS* posterior scleritis, *PsA* psoriatic arthritis, *PU* posterior uveitis, *RP* relapsing polychondritis, *RS* retrospective study, *RTI* respiratory tract infection, *SpA* spondyloarthritis, *TNF* tumor necrosis factor, *UTI* urinary tract infection

Table 2 CD-20 blockade with rituximab in patients with non-infectious scleritis

First author, year reference	Study design	N°	Type of scleritis	Systemic disease	Results/outcome measures	Safety profile	Mean follow-up (months)
Sadhu, 2020 [19]	Case series	1	PS	GPA	Clinical response, GC-sparing effect	NR	18.5 (3–36)
Murthy, 2020 [72]	Case series	1	NeS with PUK	GPA	Clinical resolution, GC-sparing effect	NR	18
Fabiani, 2020 [79]	Case series	2	Diffuse AS ($n = 1$), PS ($n = 1$)	Idiopathic ($n = 1$), GPA ($n = 1$)	Clinical resolution	No AE	21
Pérez-Jacoiste Asín, 2019 [71]	Case series	3	NS scleritis ($n = 2$) NS scleritis + episcleritis ($n = 1$)	GPA	Clinical remission	NR	50.5
Ahmed, 2019 [56]	Case series	8	AS ($n = 2$) AS and uveitis ($n = 3$) AS and PUK ($n = 2$) AS, PUK, uveitis ($n = 1$)	GPA	Clinical resolution, improvement or stabilization of visual acuity (expressed in logMAR) in 79% of the eyes. One patient experienced relapse and was re-treated with a second cycle or RTX. Four eyes with NeS required scleral-patch grafting	No side effects	46.13

Table 2 continued

First author, year reference	Study design	N°	Type of scleritis	Systemic disease	Results/outcome measures	Safety profile	Mean follow-up (months)
You, 2018 [58]	Case series	9	Diffuse AS (n = 3), Diffuse AS + PS (n = 1), Nodular AS (n = 1), NeS (n = 4), PUK (n = 4), CME (n = 3), uveitis (n = 3)	GPA	All eyes achieved remission with RTX maintenance treatment. Reduction of the modified McCluskey scale. GC-sparing effect. Mild reduction of visual acuity expressed in logMAR. No differences in intraocular pressure between baseline and last follow-up visit	Herpes zoster (n = 1), cytopenia with bronchitis and bacterial pneumonia (n = 1)	30 (median)
Fujita, 2018 [70]	Case series	1	NS scleritis + PUK + macular edema	GPA	Clinical improvement and stabilization of BCVA	NR	24
Hardy, 2017 [69]	Case series	1	NeS + PUK	RA	Clinical resolution, switch to golimumab after 2 years for suboptimal control of articular symptoms	NR	24
Fidelix, 2016 [76]	Case report	1	NAS	Surgically induced scleritis	Clinical resolution, VA	NR	6
Kasi, 2016 [68]	Case report	1	NeS, serous retinal detachment	IOI and TFIL	Improvement of symptoms and VA	NR	12

Table 2 continued

First author, year reference	Study design	N°	Type of scleritis	Systemic disease	Results/outcome measures	Safety profile	Mean follow-up (months)
Cao, 2016 [8]	Case series	15	Sectoral AS (n = 4) Diffuse AS (n = 5) Nodular AS (n = 1) NAS (n = 4), PS (n = 1)	Idiopathic (n = 4) GPA (n = 6) RA (n = 4) UMCTD (n = 1)	Favorable response in 14 patients (93.3%) and significant improvement of McCluskey grading scale for scleritis activity score at 6 months. Steroid-free remission	Infusion hypotension (n = 1)	34.1
Recillas-Gispert, 2015 [57]	Case series	8	NAS (n = 5) Nodular AS (n = 1) AS (n = 1) PS + nodular AS (n = 1)	GPA	Clear clinical improvement within 4 weeks after treatment completion, 7 out of 8 achieved remission within 7 months	Community-acquired pneumonia (n = 1)	30 (median)
Soon, 2015 [74]	Case report	1	PS	CLL	Clinical resolution, improvement of BCVA	NR	2.5
Xu, 2015 [75]	Case report	1	NS scleritis, uveitis, optic neuritis	Lymphocytic hypophysitis	Clinical resolution, improvement of VA	NR	36
Joshi, 2015 [55]	Retrospective cohort	20	NS scleritis	GPA	Complete and partial remission in 85% and 15% of patients, respectively	Infections (17 events in 6 patients, with 8% requiring hospital admission) Cytopenia (n = 2) Hypogammaglobulinemia requiring intravenous immunoglobulin (n = 2)	36.5 (median)

Table 2 continued

First author, year reference	Study design	N°	Type of scleritis	Systemic disease	Results/outcome measures	Safety profile	Mean follow-up (months)
Suhler, 2014 [6]	Clinical trial	12	AS (n = 8), AS + orbital disease (n = 2), PS (n = 1), Sclerouveitis (n = 1)	Idiopathic (n = 5), RA (n = 4), GPA and psoriasis (n = 1), Cogan's syndrome (n = 1), Systemic vasculitis (n = 1)	Reduction in scleritis grading scale, GC-sparing effect, improvement in patient and physician global health score. Seven patients experienced relapses after week 24 and received re-treatment with rituximab	Subjective increase of the size of blind spots in one patient and peri-infusional exacerbations of palmar psoriasis in another one	7
Caso, 2014 [73]	Case report	1	AS	IgG4-related disease	Clinical resolution	NR	3
Bogdanic-Werner, 2013 [67]	Case series	2	NAS (n = 1), PS (n = 1)	Idiopathic	Clinical resolution	No side effects	17.5
Morarji, 2012 [59]	Case report	1	NAS	GPA	Clinical resolution (combo therapy with IFX and RTX)	NR	12
Iaccheri, 2010 [66]	Case report	1	Nodular AS, AU, acute stromal keratitis	RA	Clinical resolution, relapse and 4th month	NR	9

Table 2 continued

First author, year reference	Study design	N°	Type of scleritis	Systemic disease	Results/outcome measures	Safety profile	Mean follow-up (months)
Bussone, 2010 [61]	Case series	2	Nodular AS ($n = 1$) AS ($n = 1$)	GPA	Clinical resolution of scleritis	CME ($n = 2$)	18
Chauhan, 2009 [62]	Case series	3	NS scleritis	RA	Clinical resolution	NR	12
Taylor, 2009 [65]	Case series	6	NAS ($n = 2$), AS ($n = 1$) AS + PS + OG ($n = 2$) PS + OG ($n = 1$)	GPA	Clinical remission	No significant side effects and no hospitalizations	12 (median)
Kurz, 2009 [64]	Case series	2	Nodular AS ($n = 1$) AS ($n = 1$)	Idiopathic scleritis ($n = 1$) RA ($n = 1$)	Clinical resolution, both patients relapsed once	Itching during infusion	24
Onal, 2008 [63]	Case report	1	NeS, AU, and ME	GPA	Clinical resolution, improvement in VA	No AE	12
Ahmadi-Simab, 2005 [54]	Case report	1	AS	Sjögren's syndrome	Resolution of symptoms and symptoms	NR	6

Table 2 continued

First author, year reference	Study design	N°	Type of scleritis	Systemic disease	Results/outcome measures	Safety profile	Mean follow-up (months)
Cheung, 2005 [53]	Case report	1	NS scleritis	GPA	Resolution of signs and symptoms on ophthalmological evaluation and GC-sparing effect	NR	7

AS anterior scleritis, *AU* anterior uveitis, *BCVA* best corrected visual acuity, *CLL* chronic lymphocytic leukemia, *CME* cystoid macular edema, *GC* glucocorticoid, *GPA* granulomatosis with polyangiitis, *IFX* infliximab, *IgG* immunoglobulin G, *IOI* idiopathic orbital inflammation, *N°* number of patients with scleritis treated with rituximab, *NAS* necrotizing anterior scleritis, *NeS* necrotizing scleritis, *NR* not reported, *NS* not specified, *OG* orbital granulomatosis, *PS* posterior scleritis, *PUK* peripheral ulcerative keratitis, *RA* rheumatoid arthritis, *RTX* rituximab, *TFIL* tumefactive fibroinflammatory lesion, *UMCTD* undifferentiated mixed connective tissue disorder, *VA* visual acuity

another retrospective study demonstrating the efficacy of TNFα blockade with IFX in refractory scleritis. A favorable response was seen in 90% of the patients, with six of them achieving remission and cessation of concomitant immunosuppressants. Dosing intervals shorter than 8 weeks were found to be well tolerated and avoid inflammatory relapses that may occur during the last days of a standard interval before the next infusion [5]. In fact, increasing the dose or shortening the interval between doses is sometime required to control scleral inflammation [5, 22, 23].

To this end, patients should be closely monitored for potential AEs. Lupus-like reactions have been described in patients treated with IFX for severe scleritis [5, 22]. Patients treated with IFX may also develop new ocular inflammations defined as a paradoxical reaction. Possible mechanisms underlying such reactions may include interferon overproduction, Th17 cell expansion, and Th1 homing due to increased chemokine levels and receptors induced by interferon-α [24].

Murphy et al. reported seven IFX-treated patients with non-infectious ocular inflammatory disease refractory to conventional immunosuppression, of whom four were diagnosed with scleritis. Three out of four achieved remission, with the remaining patient showing a partial response but withdrawn from treatment because of an infusion-related reaction. Given its rapid action, the authors suggested IFX as a valid substitute for high-dose prednisolone as rescue therapy during ocular relapses [25]. A small series of three patients affected by idiopathic necrotizing anterior scleritis showed an excellent efficacy of IFX characterized by a complete clinical response as well as resolution of choroidal and retinal detachment [26]. Fifteen additional single-patient reports were retrieved [27–41], and their respective findings are reported in Table 1. IFX has proven to be effective in the treatment of refractory scleritis also associated with rare disorders such as RP [33, 43], granulomatosis with polyangiitis (GPA) [29, 39], and surgically induced necrotizing scleritis [32] as well as in pediatric patients under appropriate circumstances [31, 39, 41].

Table 3 Anti-IL-1 agents, tocilizumab, ustekinumab, abatacept, daclizumab, and alemtuzumab treatment in non-infectious scleritis

First author, year reference	Study design	Biologic agent/small molecule, N	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Farhat, 2021 [84]	Case series	TCZ (n = 3)	Diffuse AS (n = 2, 1 with concomitant uveitis) Nodular AS + uveitis (n = 1)	RP	Complete resolution of scleritis	Transient neutropenia (n = 1)	20
Fabiani, 2020 [79]	Case series	ANA (n = 3) ABA (n = 3) TCZ (n = 2) TFC (n = 1)	Nodular AS (n = 1) PS (n = 2) Diffuse AS (n = 6)	Idiopathic (n = 1) RA (n = 6) FMF (n = 1) Psoriatic arthritis (n = 1)	Significant decrease in scleritis grading in the number of relapses, GC-sparing effect and stable VA	No AE	16 for ANA 31.7 for ABA 15.5 for TCZ 6 for TFC
Pyare, 2020 [94]	Case report	TFC (n = 1)	Necrotizing AS	Idiopathic	Resolution of scleral inflammation and remarkable improvement of symptom within 1 month of treatment	Tolerated and no AE	NR
Poelman, 2020 [83]	Case report	TCZ (n = 1)	AS	GCA	Rapid and sustained remission	No AE	12
Matsumoto, 2020 [89]	Case series	Ustekinumab (n = 1)	NS scleritis	Spondyloarthritis with Crohn's disease	Clinical improvement	NR	NR

Table 3 continued

First author, year reference	Study design	Biologic agent/small molecule, N	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Iwahashi, 2019 [24]	CS	TCZ (n = 1)	AS + macular edema	RA	Complete resolution after a paradoxical posterior inflammation induced by infliximab	NR	12
Paley 2018 [93]	Case report	TFC (n = 1)	NS scleritis	Idiopathic	Resolution of scleritis within 3 weeks	NR	9
Bottin, 2018 [9]	Pilot study	ANA (n = 10)	AS (n = 7), AS + PS (n = 3), PUK (n = 1), Uveitis, macular edema, and keratitis (n = 1)	Idiopathic (n = 4), RP (n = 3), RA (n = 1), Psoriatic arthritis (n = 1), Behçet syndrome (n = 1)	Clinical remission in 8 patients within 1 month and in one additional patient within 2 months, significant decrease in ocular relapse rate, GC-sparing effect	ISR (n = 4), Dental abscess (n = 1)	19.4
Michael, 2017 [86]	Case report	TCZ (n = 1)	Nodular AS	RA, pyoderma gangrenosum, and SLE	Paradoxical reaction to TCZ. Complete resolution after TCZ withdrawal at 9 months	Nodular AS	–
Shimizu, 2017 [85]	Case report	TCZ (n = 1)	AS	RP	Sustained remission	NR	14
Knickelbein, 2016 [10]	Clinical trial	Gevokizumab (n = 8)	AS (n = 8)	Idiopathic (n = 6), RA (n = 1), LES and SS (n = 1)	Most eyes (7/9) met the primary outcome with reduction of scleral inflammation grading No changes in intraocular pressure and stable visual acuity	No serious AE, ISR (n = 1), elevated liver enzymes (n = 1), irritable bowel syndrome (n = 3), hypotension (n = 1)	12

Table 3 continued

First author, year reference	Study design	Biologic agent/small molecule, N	Type of scleritis	Systemic disease	Results	Safety profile	Mean follow-up (months)
Silpa-Archa, 2016 [82]	Case series	TCZ (n = 6)	AS (n = 5), AS + PS (n = 1)	RA (n = 4), Inflammatory bowel disease (n = 1), Idiopathic (n = 1)	Inflammatory control with GC-sparing success in 50% of patients at 9 months and a faster response compared to patients with uveitis	Chest tightness at first 6 h after infusion (n = 1), Serious AE (n = 1)	14.5
Tode, 2015 [81]	Case report	TCZ (n = 1)	Necrotizing AS	Idiopathic	Clinical resolution, stable VA	NR	24
Kommaraju, 2014 [91]	Case report	Alemtuzumab (n = 1)	Diffuse AS	T cell prolymphocytic leukemia	Clinical improvement	Death due to the systemic disease	19
Botsios, 2007 [78]	Case series	ANA (n = 2)	Diffuse AS	RA	Clinical remission and improvement in VA. Dose reduction to alternate days in one patient, caused a scleritis relapse	NR for ANA. Paradoxical diffuse AS under etanercept therapy in 1 patient	24
Papaliodis, 2003 [90]	Case series	Daclizumab (n = 2)	NS scleritis	NS	improvement in inflammation in 1/2	No serious AE	11

ABA abatacept, *AE* adverse event, *ANA* anakinra, *AS* anterior scleritis, *FMF* familial Mediterranean fever, *GC* glucocorticoid, *GPA* granulomatosis with polyangiitis, *ISR* injection-site reaction, *NR* not reported, *NS* not specified, *PS* posterior scleritis, *PUK* peripheral ulcerative keratitis, *RA* rheumatoid arthritis, *RP* relapsing polychondritis, *SLE* systemic lupus erythematosus, *SS* Sjögren's syndrome, *TCZ* tocilizumab, *TFC* tofacitinib, *VA* visual acuity

Direct comparisons between ADA and IFX are currently limited. Ragam et al. found that the overall likelihood of achieving inflammation control on ADA and IFX was 66% and 77%, respectively, without any significant differences [7]. The lack of robust data does not allow one to establish the superiority of one agent over the other in the therapeutic approach of non-infectious scleritis. Moreover, in-class switching is a suitable solution in case loss of efficacy or safety concerns arise [7, 18].

Etanercept

Etanercept (ETN), either in association with conventional immunosuppressants or as monotherapy, has provided encouraging results in the early 2000s for the management of diffuse or necrotizing anterior scleritis as well as sterile peripheral ulcerative keratitis (PUK). Particularly, ETN was shown to control inflammation and arrest tissue ulceration while permitting a drug-sparing effect in 10 patients affected by non-infectious scleritis or PUK [42]. Its use, however, has lost popularity over time given the reported paradoxical effects on ocular inflammatory diseases. Indeed, several studies have disclosed controversial results of ETN in the management of such conditions. The first cases of paradoxical ocular inflammation were reported by Smith and colleagues. Three patients with RA developed bilateral scleritis for the first time, 1, 2, and 6 months after commencing ETN, respectively [43]. Another study performing direct comparisons between IFX and ETN reported two other patients with RA developing their first episode of anterior scleritis after ETN initiation. Furthermore, all ETN-treated patients in the study eventually required a change in medication to control ocular inflammation. The authors found IFX to be superior to ETN in the treatment of ocular inflammation and in decreasing the use of topical GCs [44]. Other single-patient reports and small case series of patients with RA have reported similar findings, raising the dilemma of whether to continue treatment with ETN despite an optimal control of extraocular manifestations [45–48]. To the best of our knowledge, a total of 13 patients with ETN-related paradoxical scleritis, all affected by RA, have been described so far. The underlying mechanisms still need to be clarified, but a possible pathogenetic hypothesis may explain the tendency of TNF inhibition to precipitate an ocular inflammatory disease in predisposed individuals. First of all, TNF inhibition may interfere with apoptosis, which is believed to play a crucial role in the maintenance of ocular immune privilege [49]. Secondly, pharmacodynamic peculiarities may become relevant in specific situations. For instance, when TNFα levels are low, p75 TNF receptor, which possesses a fivefold higher affinity than p55, facilitates p55 activity possibly by a ligand-passing mechanism or as a result of intracellular kinase activation. Therefore, ETN, a soluble P75 TNF receptor, may interfere with immune homeostasis and influx of inflammatory cells in the eye [47]. Further data are required to draw firm conclusions in such a controversial topic.

Golimumab

Experience with golimumab (GOL) in treating non-infectious scleritis relies on rare single-patient reports [11, 50, 51]. GOL efficacy was described in a middle-aged woman affected by psoriatic arthritis and bilateral progressive necrotizing posterior scleritis associated with retinal vasculitis refractory to methotrexate, cyclosporine, and ADA treatment. Following the introduction of GOL, good control of the scleritis and arthritis without any relapse or progression of retinal lesions was described [50]. GOL proved to be rapidly effective in controlling scleral inflammation also in a patient affected by necrotizing scleritis and advanced glaucoma requiring Ahmed valve implant. Resolution of scleritis within 2 months allowed the insertion of an Ahmed valve in this patient, avoiding the high risk of globe perforation due to scleral thinning and a post-surgical relapse of scleritis [51].

Certolizumab Pegol

No comprehensive studies describing the treatment of scleritis with certolizumab have been reported so far, although a single case report described its efficacy in a case of rheumatoid arthritis (RA)-related bilateral scleritis refractory to ETN and following withdrawal of IFX because of AEs [52].

ANTI-CD20 THERAPY

Rituximab

Since the first reports of rituximab (RTX) efficacy in scleritis associated with systemic disorders [53, 54], a growing body of evidence in the management of refractory scleritis with RTX has emerged in the last 15 years. The only prospective, randomized, phase I/II clinical trial published so far disclosed an optimal RTX efficacy and safety profile in a large proportion of patients affected by refractory non-infectious scleritis, with nine out of 12 achieving a reduction of scleritis grading scale within 24 weeks. More than half of them required retreatment to maintain inflammatory control. Interestingly, the authors did not find notable differences in terms of efficacy, safety, and B cell depletion between patients who received 500 mg and those treated with 1000 mg, suggesting that treatment regimens with lower dosages may be therapeutically equivalent to the standard protocol employed in many rheumatologic diseases [6]. However, the vast majority of the available data relies on real-life uncontrolled scenarios. Joshi and coworkers conducted a retrospective analysis of 37 patients with GPA treated with RTX, of whom 20 were diagnosed with scleritis. RTX was shown to induce complete and partial remission in 85% and 10% of patients, respectively, at 6 months [55]. Regarding cyclophosphamide use in GPA-related scleritis, RTX appeared to be superior in terms of safety and efficacy, with less need for treatment interruptions and dose adjustments, although both therapies proved to be effective and safe [56]. RTX was administered according to the rheumatologic protocol in eight patients with GPA-related refractory scleritis with optimal results [57]. A different posologic regimen may be required to maintain GC-free drug-induced remission in recalcitrant scleritis [8]. Yet, no firm conclusions can be drawn in this regard as the small case series reported do not allow head-to-head comparisons for the different protocols employed. A second cycle of RTX may be administered in case of relapse [6, 56, 57]. In fact, a considerable proportion of patients with GPA and scleritis have experienced relapses, thus advocating for a maintenance treatment instead of a single course of RTX that should be extended for at least 18 months in order to lower the relapse rate [58]. Morarji and colleagues described a unique and successful combination therapy of RTX with IFX. The patient affected by GPA received IFX during early stages whilst waiting for RTX to establish disease remission and, as a result, avoiding cyclophosphamide in the acute phase [59]. Potential usefulness of IFX in gaining rapid disease control and allowing time for RTX to take effect, at least in some patients with necrotizing scleritis, may be interesting to explore while controlling for AEs. A case of *Pneumocystis jirovecii* pneumonia after RTX therapy and prednisolone for posterior scleritis has been described [60]. Additionally, paradoxical ocular manifestations including cystoid macular edema following RTX administration were also reported [61].

Along with its efficacy in most patients with localized and generalized ocular GPA, RTX is an effective treatment modality for recalcitrant non-infectious scleritis either idiopathic or associated with different systemic inflammatory disorder. It may also provide long-term drug-free remission in some patients. In a relatively large cohort of patients, 14 out of 15 (93.3%) showed an initial improvement, and a subgroup analysis among those with longer follow-up disclosed a success rate of 61% [8]. Table 2 lists all studies published so far where RTX has been employed to treat non-infectious scleritis and details some data regarding ocular and systemic diagnosis, main findings, mean follow-up as well as safety profile if reported. Briefly, most patients with scleritis treated with RTX were

affected by GPA ($n = 68$), followed by RA ($n = 14$) and idiopathic cases ($n = 13$). Most patients were diagnosed with diffuse anterior scleritis ($n = 36$), followed by necrotizing anterior scleritis ($n = 22$), posterior scleritis or pan-scleritis ($n = 11$), and nodular anterior scleritis ($n = 5$). However, the anatomical pattern was not specified in a considerable proportion of cases ($n = 30$). The first study of scleritis associated with RA and successfully treated with RTX dates back to 2009. The authors described three patients refractory or intolerant to conventional immunosuppressants or TNF inhibitors, suggesting a special consideration for RTX in inflammatory eye diseases secondary to RA or other rheumatologic disorders [62]. Other interesting case reports and small case series have also been reported [19, 63–72]. RTX yielded a rapid benefit in an interesting case of severe and refractory scleritis associated with IgG4-related disease and initially misdiagnosed as idiopathic scleritis, advocating for a potential role of CD20 blockade as a therapeutic option in such cases [73]. Anecdotal evidence has been disclosed for RTX efficacy in scleritis diagnosed in the context of chronic lymphatic leukemia [74], lymphocytic hypophysitis [75], and surgically induced scleritis [76]. RTX appears to be a promising agent in the management of refractory scleritis in both idiopathic scleritis and scleritis associated with immune-mediated systemic disorders. Its administration, either as monotherapy or in combination with GCs or immunosuppressive agents, has shown a favorable ocular outcome. It would be tempting to test RTX efficacy as a first-line immunosuppressive therapy instead of a last resort option in the classic stepwise/stepladder approach in selected young patients with a particular severe form [67, 72].

IL-1 INHIBITORS

Interleukin (IL)-1 plays a key role in the pathogenesis of different inflammatory and degenerative eye diseases and its overexpression might be an initiating factor for many immunopathologic scenarios in the eye, as proven by the efficacy of the specific IL-1 blockade in different ocular conditions [77].

Anakinra

Botsios et al. described two patients affected by unilateral refractory non-infectious anterior scleritis related to RA and treated with anakinra (ANA) in combination with methotrexate 10 mg/week over a follow-up period of 3 years (patient 1) and 1 year (patient 2). Former IFX and ETN improved the articular domain, but did not ameliorate scleral inflammation. Both patients experienced a dramatic resolution of scleritis signs and symptoms within 6–8 weeks [78]. Treatment with the IL-1 receptor antagonist ANA was later employed in 10 consecutive patients affected by severe and refractory non-necrotizing scleritis. Seven patients presented bilateral anterior non-necrotizing diffuse scleritis while three patients manifested unilateral disease either with anterior or posterior involvement. Ninety percent of the patients were considered as complete responders at the end of follow-up. Remission, defined as resolution of scleral inflammation, edema, and pain, occurred after 1 month of ANA treatment in eight patients and after 2 months in one patient. Interestingly, a drug-sparing effect was recorded with a significant reduction of GC daily intake as well as discontinuation of conventional immunosuppressants in all but one. In addition to a rapid improvement of scleral inflammation within 1 month in almost all patients, the authors described a good safety profile with only four mild AEs that did not require ANA discontinuation [10]. We recently reported 14 patients with scleritis treated with biologic agents other than TNFα inhibitors. Three patients were administered ANA 100 mg/day subcutaneously. One of them has been receiving ANA for 44 months with resolution of scleral inflammation and scleritis relapses [79].

Gevokizumab

Blockade of IL-1β with gevokizumab has been shown to provide benefits in treating active,

non-infectious, anterior scleritis. More extensively, gevokizumab has been used in a phase I/II clinical trial where seven out of eight patients with active non-infectious, non-necrotizing scleritis met the primary outcome. Seven eyes from seven patients exhibited at least a two-step reduction or reduction to grade 0 in scleral inflammation on a 0 to +4 scale according to a standardized photographic scleritis grading system within a median time of 2 weeks. Moreover, a good safety profile was reported [10].

ANTI-IL-6 THERAPY

Tociluzimab

Pathogenetic evidence linking IL-6 with intraocular inflammation has paved the way for newer treatment strategies. Indeed, manipulation of IL-6 in the inflammatory cascade of immune-driven uveitis has yielded encouraging results [80]. However, data on scleritis are still scarce and IL-6 inhibition in this sight-threatening disorder is still based on small case series and single-patient reports. Tode et al. [81] reported the first case of successful anti-IL6 treatment in refractory unilateral anterior necrotizing scleritis. The patient showed a reduction in scleritis grade and the necrotic process ceased. Scleritis remission was achieved after six combined steroid and tocilizumab (TCZ) infusions. Nearly a year later, a retrospective case series of 17 patients, six of whom were affected by recalcitrant non-infectious scleritis (anterior scleritis $n = 5$, panscleritis $n = 1$, eight eyes), was published. Five patients were diagnosed with an underlying systemic disease. At 6- and 9-month follow-up, 50% of patients with scleritis achieved control of inflammation as well as a steroid-sparing effect. Additionally, TCZ was able to control disease activity in one patient with scleritis and inflammatory bowel disease for almost 3 years before being discontinued because of secondary failure. Interestingly, in a subgroup analysis, time to inflammatory control of scleritis was found to be shorter than that of the patients affected by uveitis with a median time of

50 days and 140 days, respectively [82]. Since then, three other cases have been reported by different authors. Poelman et al. [83] described a case of a scleritis associated with biopsy-proven giant cell arteritis rapidly and persistently responsive to TCZ. We reported two patients treated with TCZ for 3 and 28 months, respectively, achieving resolution of the diffuse anterior scleritis in the affected eyes [79].

TCZ seems to be a promising treatment also for RP-related scleritis either as a first-line immunosuppressive treatment or in refractory patients unresponsive to conventional immunosuppressants and/or other biologic agents. A recent retrospective study of consecutive cases of scleritis and sclerouveitis showed that they optimally responded to TCZ after failing several conventional disease modifying anti-rheumatic drugs (cDMARDs) and biologic agents. Three patients clinically diagnosed with RP and recalcitrant anterior diffuse or nodular scleritis (five eyes) received monthly treatment with TCZ at a dose of 8 mg/kg. This approach resulted in complete and sustained ocular and extraocular remission up to 2 years, while allowing a steroid-sparing effect [84]. Another patient with RP-related scleritis and treated with TCZ has been reported. The report describes a case with bilateral scleritis and auricular chondritis refractory to GCs, methotrexate, and IFX that was successfully treated with TCZ [85]. Paradoxical reactions might also be possible. Anterior nodular scleritis following the second dose of TCZ therapy and responsive to orally administered prednisone was diagnosed in a patient with rheumatoid arthritis, pyoderma gangrenosum, and systemic lupus erythematosus. Hence, ocular manifestations following IL-6 inhibition, although rare, should be considered as potential AEs when treating rheumatic patients with inflammatory arthritis [86].

OTHER BIOLOGICS AGENTS AND TARGETED SMALL MOLECULES

Abatacept

Fabiani et al. employed co-stimulatory signal modulation with abatacept in patients with scleritis affected by RA. Two of three patients (four eyes) with active diffuse anterior scleritis achieved resolution of ocular inflammation at last follow-up visit [79]. Abatacept efficacy has also been reported in other ocular inflammatory conditions such as PUK [87] and in juvenile idiopathic arthritis-related uveitis also refractory to TNFα inhibitors [88]. Further prospective and well-designed studies are warranted to confirm these preliminary findings.

Ustekinumab

Ustekinumab is a human monoclonal antibody directed against the shared p40 subunit of IL-12 and IL-23 licensed for psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. Currently, no randomized clinical trials describing the effects of ustekinumab on scleritis have been reported. Its efficacy was described in a case of spondyloarthritis associated with Crohn's disease where also extraintestinal manifestations, including scleritis, resolved shortly after the drug was initiated [89].

Daclizumab

Daclizumab is a humanized monoclonal antibody acting against the α-subunit-CD25 of the IL-2 receptor. In particular, it recognizes the high-affinity protein Tac-p55 of the IL-2 receptor and inhibits IL-2 signaling on activated T cells and thus has the potential to restore homeostasis of a dysregulated immune system. Daclizumab was shown to improve inflammation in one of two patients with scleritis in a retrospective case series analyzing its efficacy in various ophthalmologic inflammatory conditions refractory to standard therapy [90]. In March 2018, this drug was withdrawn from the market because of reports of autoimmune encephalitis.

Alemtuzumab

Kommaraju and colleagues reported a case of T cell prolymphocytic leukemia with central nervous system involvement that presented with bilateral diffuse anterior scleritis and anterior uveitis with secondary glaucoma. Systemic treatment with alemtuzumab and intrathecal therapies with alternating cytarabine/hydrocortisone and methotrexate/hydrocortisone improved the lymphadenopathy while resolving the pleural effusion and the ophthalmologic manifestations within 1 month. However, unresponsive central nervous system involvement was responsible for the fatal outcome 19 months thereafter [91].

Tofacitinib

Intracellular signaling pathways, such as those concerning Janus kinase (JAK), have emerged as a key axis in the cytokine network and, consequently, as important therapeutic targets. Tofacitinib is an oral reversible JAK inhibitor classified among targeted small molecules [92]. Its effectiveness in refractory scleritis has been suggested in single-patient reports [79, 93], including cases with necrotizing scleritis [94]. The underlying biologic rationale relies on the tight interplay between JAK/signal transducers and activators of transcription (STAT) intracellular pathways and inflammatory cytokines such as TNF and IL-6 which are involved in the pathogenesis of ocular inflammatory diseases. Paley et al. described two cases of recalcitrant uveitis and scleritis responsive to tofacitinib after failure or intolerance to multiple immunomodulatory regimes. One patient with scleritis responded within 3 weeks of tofacitinib treatment [93]. A similar time to response was also observed in an Indian patient affected by necrotizing scleritis [94]. Patients who are refractory to treatment with oral GCs and immunomodulatory drugs including biologic agents can benefit from this new class of small molecules that may therefore be employed as

effective GC-sparing agents. However, further studies are warranted to confirm these anecdotal findings.

Table 3 provides all the available studies with some of their respective main findings regarding IL-1 inhibitors, TCZ, and other biologic agents as well as small molecules employed in non-infectious scleritis.

CLOSING REMARKS

The management of non-infectious scleritis may be challenging since its immunopathogenesis is not completely understood. Both innate and adaptive immunity may be advocated as the driving mechanisms leading to tissue damage, with a pivotal role played by inflammatory cytokines such as TNFα and IL-1, which in turn induce the secretion of matrix metalloproteinases from infiltrating inflammatory cells and stromal scleral fibroblasts [1]. Despite being hard to pinpoint where non-infectious scleritis is exactly situated in the immunological disease continuum [95], it is safe to assume that the pathophysiological mechanisms are largely dependent on the underlying systemic disease, if present. Indeed, many authors believe that non-infectious scleritis associated with systemic disorders represents an immune complex-mediated condition, whereas idiopathic scleritis may arise after a delayed hypersensitivity reaction [96]. The association with systemic diseases may have prognostic implications as well. Berkenstock and Carey conducted the largest retrospective review currently described in the literature to evaluate the association between scleritis and autoimmune entities. They reviewed 5.9 million charts of the electronic medical record and found 2702 patients affected by scleritis, of which approximately a third (31.4%) had an underlying autoimmune disease [97]. In this analysis, the most frequent associated autoimmune condition was RA (6.8%) followed by HLA-B27-related diseases (5.7%) and Sjögren/Sicca syndrome (4.5%), gout (3.5%), lupus (3.0%), and granulomatosis with polyangiitis (1.7%). Scleritis associated with systemic conditions, especially those affected by ANCA-associated vasculitis, appears to have a worse visual prognosis [98], making early diagnosis a crucial step for its successful management. The underlying systemic disease may also be considered as a driving factor in the choice of the more appropriate biologic for the management of scleritis. For instance, RTX may be particularly effective in the treatment of scleritis associated with systemic vasculitis. A better understanding of the pathogenesis of ocular inflammatory diseases and the development of new molecules have enriched the therapeutic armamentarium and created more effective treatment approaches. Anti-TNFα monoclonal antibodies, IL-1 and IL-6 inhibitors as well as anti-CD20 RTX were shown to control scleral inflammation and reduce the overall scleritis relapses, thus allowing a GC-sparing effect. Visual acuity is generally preserved and few adverse reactions have been reported [7, 8, 10, 11, 79]. Given the lack of robust evidence-based data, with the available literature reported so far and based on our personal experience, we suggest that TNFα inhibitors such as ADA or IFX should be trialed as first-line biologic agents unless the specific underlying systemic disease warrants otherwise. Non-responsive patients and/or those suffering from RA may benefit from IL-1 inhibitors or RTX. Other biologic agents including abatacept and ustekinumab or JAK inhibitors may be useful additions to the treatment armamentarium for refractory scleritis.

Another key aspect to consider is the potential difference between biologic monotherapy and combination therapy with cDMARDs. It is indeed still unclear whether concomitant treatment with cDMARDs may add clinical benefit and ultimately improve the overall prognosis of patients with scleritis. In a retrospective study of 17 patients with non-infectious, non-necrotizing scleritis treated with TNFα inhibitors, 11 patients were found to fail previous therapies with cDMARDs and 12 of them were receiving combination therapy while five were able to achieve clinical response with an TNFα inhibitor alone [7]. Sobrin et al. reported five out of 10 patients with scleritis treated with IFX being able to reduce or discontinue concurrent treatment with cDMARDs
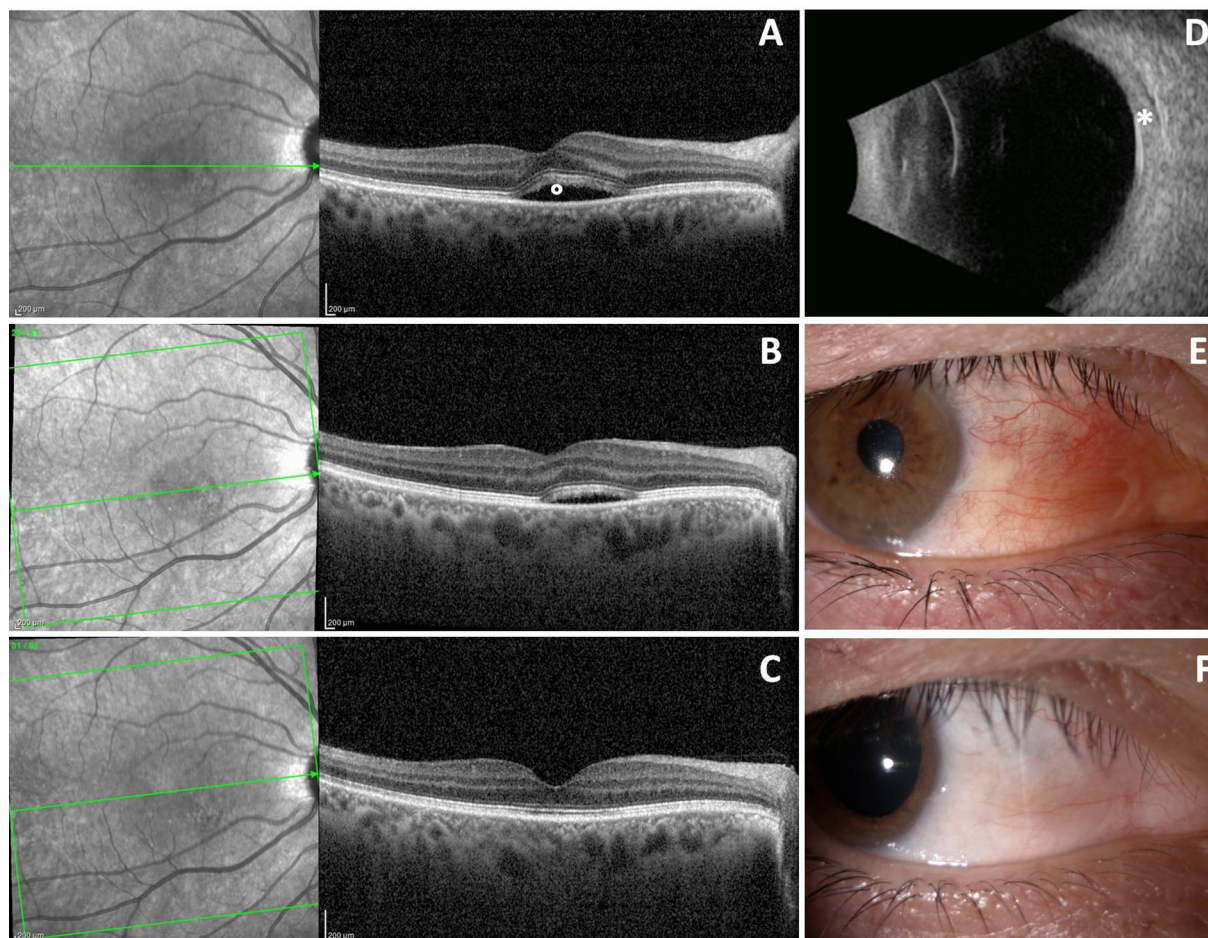
Fig. 1 Posterior and anterior unilateral (right eye) refractory scleritis in a patient affected by psoriatic arthritis undergoing subcutaneous treatment with monoclonal TNF inhibitor golimumab 50 mg every 28 days. Ocular ultrasonography (**d**) shows a circular acoustically hollow area called the ring sign corresponding to an edematous Tenon capsule (*), typical signs of an active posterior scleritis. Optical coherence tomography (OCT) scans show the presence of a concomitant subfoveal exudative neuroepithelium detachment (°) in the same eye (**a**) that decreased following 2 months of biologic treatment along with a short course of oral glucocorticoids (**b**), and totally disappeared after 4 months of treatment (**c**). Anterior segment photograph (**e**) shows the concomitant active anterior scleritis inflammation and its resolution after 2 months treatment (**f**)

[22]. Other studies have reported different proportions of patients requiring concomitant cDMARDs, ranging from 10% [9] to more than 70% [11]. Cao et al. [8] described 13 out of 15 patients with scleritis achieving a scleritis grading score of 0 at 6 months during treatment with RTX: six patients using RTX in monotherapy and seven as combination therapy with another agent. Conversely, Joshi et al. found RTX to be effective in achieving remission in patients with GPA, but all of them

required a maintenance treatment with cDMARDs [55]. Most of the patients receiving biologic agents or small molecules were previously treated with cDMARDs. Given the lack of response to monotherapy with cDMARDs, it can be safely assumed that the subsequent treatment with biologic agents was the one determining the improvement/resolution of scleritis. However, treatment should be ideally tailored according to the patient's profile. Patients diagnosed with scleritis and an

underlying associated systemic immune disease or those with a particularly active and severe disease may require an aggressive combination therapy to avoid long-term ocular and extraocular complications (Fig. 1). Studies specifically investigating this crucial endpoint are needed to fully explore the efficacy of monotherapy with biologic agents and their ability to decrease the immunosuppressive load.

Aggressive and early treatment is warranted to achieve rapid remission, prevent relapses visual acuity, and ultimately avoid long-term structural irreversible complications. Management of scleritis must take place in a multidisciplinary setting in order to maximize treatment benefits while minimizing safety issues. A future goal would be to tailor treatment strategies according to each patient's needs and ideally associate patients' ocular and systemic profiles with specific cytokine inhibitors. Biologic agents and small molecules represent a milestone for scleritis treatment but deserve further investigation in properly designed and powered studies to provide more robust evidence in terms of efficacy, optimal dosage regimen, and hopefully address some of the unmet needs in such a sight-threatening condition.

ACKNOWLEDGEMENTS

REFERENCES

1. Wakefield D, Di Girolamo N, Thurau S, Wildner G, McCluskey P. Scleritis: immunopathogenesis and molecular basis for therapy. Prog Retin Eye Res. 2013;35:44–62. https://doi.org/10.1016/j.preteyeres.2013.02.004.

2. Beardsley RM, Suhler EB, Rosenbaum JT, Lin P. Pharmacotherapy of scleritis: current paradigms and future directions. Expert Opin Pharmacother.

2013;14(4):411–24. https://doi.org/10.1517/14656566.2013.772982.

3. Nevares A, Raut R, Libman B, Hajj-Ali R. Noninfectious autoimmune scleritis: recognition, systemic associations, and therapy. Curr Rheumatol Rep. 2020;22(4):11. https://doi.org/10.1007/s11926-020-0885-y.

4. Roufas A, Jalaludin B, Gaskin C, McCluskey P. Subconjunctival triamcinolone treatment for nonnecrotising anterior scleritis. Br J Ophthalmol. 2010;94(6):743–7. https://doi.org/10.1136/bjo.2009.164962.

5. Doctor P, Sultan A, Syed S, Christen W, Bhat P, Foster CS. Infliximab for the treatment of refractory scleritis. Br J Ophthalmol. 2010;94(5):579–83. https://doi.org/10.1136/bjo.2008.150961.

6. Suhler EB, Lim LL, Beardsley RM, et al. Rituximab therapy for refractory scleritis: results of a phase I/II dose-ranging, randomized, clinical trial. Ophthalmology. 2014;121(10):1885–91. https://doi.org/10.1016/j.ophtha.2014.04.044.

7. Ragam A, Kolomeyer AM, Fang C, Xu Y, Chu DS. Treatment of chronic, noninfectious, nonnecrotizing scleritis with tumor necrosis factor alpha inhibitors. Ocul Immunol Inflamm. 2014;22(6):469–77. https://doi.org/10.3109/09273948.2013.863944.

8. Cao JH, Oray M, Cocho L, Foster CS. Rituximab in the treatment of refractory noninfectious scleritis. Am J Ophthalmol. 2016;164:22–8. https://doi.org/10.1016/j.ajo.2015.12.032.

9. Bottin C, Fel A, Butel N, et al. Anakinra in the treatment of patients with refractory scleritis: a pilot study. Ocul Immunol Inflamm. 2018;26(6):915–20.

10. Knickelbein JE, Tucker WR, Bhatt N, et al. Gevokizumab in the treatment of autoimmune nonnecrotizing anterior scleritis: results of a phase I/II clinical trial. Am J Ophthalmol. 2016;172:104–10. https://doi.org/10.1016/j.ajo.2016.09.017.

11. Fabiani C, Sota J, Sainz-de-la-Maza M, et al. Effectiveness of TNF-α blockade in the treatment of refractory non-infectious scleritis: a multicentre study. Clin Exp Rheumatol. 2020;38(6):1138–44.

12. Huynh N, Cervantes-Castaneda RA, Bhat P, Gallagher MJ, Foster CS. Biologic response modifier therapy for psoriatic ocular inflammatory disease. Ocul Immunol Inflamm. 2008;16(3):89–93. https://doi.org/10.1080/09273940802023786.

13. Restrepo JP, Molina MP. Successful treatment of severe nodular scleritis with adalimumab. Clin Rheumatol. 2010;29(5):559–61. https://doi.org/10.1007/s10067-009-1368-8.

14. Bawazeer AM, Raffa LH. Adalimumab in the treatment of recurrent idiopathic bilateral nodular scleritis. Oman J Ophthalmol. 2011;4(3):139–41. https://doi.org/10.4103/0974-620X.91271.

15. Akhtar S, Babar S, Lightman S, Mason JC. Adalimumab-induced remission of anterior scleritis: a very rare late manifestation of Takayasu arteritis. Rheumatol (Oxford). 2015;54(12):2288–90. https://doi.org/10.1093/rheumatology/kev324.

16. Lawuyi LE, Gurbaxani A. Refractory necrotizing scleritis successfully treated with adalimumab. J Ophthalmic Inflamm Infect. 2016;6(1):37. https://doi.org/10.1186/s12348-016-0107-y.

17. Durrani K, Kempen JH, Ying GS, et al. Systemic immunosuppressive therapy for eye diseases site research group. Adalimumab for ocular inflammation. Ocul Immunol Inflamm. 2017;25(3):405–12. https://doi.org/10.3109/09273948.2015.1134581.

18. Sharma SM, Damato E, Hinchcliffe AE, et al. Long-term efficacy and tolerability of TNFα inhibitors in the treatment of non-infectious ocular inflammation: an 8-year prospective surveillance study. Br J Ophthalmol. 2019;2019:312767. https://doi.org/10.1136/bjophthalmol-2018-312767.

19. Sadhu S, Dutta Majumder P, Biswas J. Biological therapy in refractory cases of uveitis and scleritis: an analysis of 18 cases from a tertiary eye care center from South India. Indian J Ophthalmol. 2020;68(9):1929–33. https://doi.org/10.4103/ijo.IJO_966_20.

20. Sainz-de-la-Maza M, Molina N, Gonzalez-Gonzalez LA, Doctor PP, Tauber J, Foster CS. Scleritis associated with relapsing polychondritis. Br J Ophthalmol. 2016;100(9):1290–4. https://doi.org/10.1136/bjophthalmol-2015-306902.

21. Sen HN, Sangave A, Hammel K, Levy-Clarke G, Nussenblatt RB. Infliximab for the treatment of active scleritis. Can J Ophthalmol. 2009;44(3):e9–12. https://doi.org/10.3129/i09-061.

22. Sobrin L, Kim EC, Christen W, Papadaki T, Letko E, Foster CS. Infliximab therapy for the treatment of refractory ocular inflammatory disease. Arch Ophthalmol. 2007;125(7):895–900. https://doi.org/10.1001/archopht.125.7.895.

23. Ashok D, Ayliffe WH, Kiely PD. Necrotizing scleritis associated with rheumatoid arthritis: long-term remission with high-dose infliximab therapy. Rheumatol (Oxford). 2005;44(7):950–1. https://doi.org/10.1093/rheumatology/keh635.

24. Iwahashi C, Ono H, Haruta M, et al. New onset or exacerbation of uveitis with infliximab: paradoxical effects? BMJ Open Ophthalmol. 2019;4(1): e000250. https://doi.org/10.1136/bmjophth-2018-000250.

25. Murphy CC, Ayliffe WH, Booth A, Makanjuola D, Andrews PA, Jayne D. Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. Ophthalmology. 2004;111(2):352–6. https://doi.org/10.1016/S0161-6420(03)00721-8.

26. Ahn SJ, Oh JY, Kim MK, Wee WR. Treating refractory scleritis with infliximab. Jpn J Ophthalmol. 2009;53(3):286–7. https://doi.org/10.1007/s10384-008-0652-5.

27. Díaz-Valle D, Miguélez Sánchez R, Fernández Espartero MC, Pascual AD. Tratamiento de la escleritis anterior difusa refractaria con infliximab [Treatment of refractory anterior diffuse scleritis with infliximab]. Arch Soc Esp Oftalmol. 2004;79(8):405–8. https://doi.org/10.4321/s0365-66912004000800010.

28. Cazabon S, Over K, Butcher J. The successful use of infliximab in resistant relapsing polychondritis and associated scleritis. Eye (Lond). 2005;19(2):222–4. https://doi.org/10.1038/sj.eye.6701457.

29. El-Shabrawi Y, Hermann J. Anti-TNF alpha therapy in chronic necrotizing scleritis resistant to standard immunomodulatory therapy in a patient with Wegener's granulomatosis. Eye (Lond). 2005;19(9): 1017–8. https://doi.org/10.1038/sj.eye.6701712.

30. Atchia II, Kidd CE, Bell RW. Rheumatoid arthritis-associated necrotizing scleritis and peripheral ulcerative keratitis treated successfully with infliximab. J Clin Rheumatol. 2006;12(6):291–3. https://doi.org/10.1097/01.rhu.0000249766.24780.95.

31. Weiss K, Rieger R, Keitzer R, Pleyer U. Successful infliximab treatment of posterior scleritis in a 13-year-old child refractory to other immunosuppressive therapy. Graefes Arch Clin Exp Ophthalmol. 2007;245(11):1735–7. https://doi.org/10.1007/s00417-007-0634-1.

32. Morley AM, Pavesio C. Surgically induced necrotising scleritis following three-port pars plana vitrectomy without scleral buckling: a series of three cases. Eye (Lond). 2008;22(1):162–4. https://doi.org/10.1038/sj.eye.6702708.

33. Culver EL, Salmon JF, Frith P, Travis SP. Recurrent posterior scleritis and orbital myositis as extra-intestinal manifestations of Crohn's disease: case report and systematic literature review. J Crohns Colitis. 2008;2(4):337–42. https://doi.org/10.1016/j.crohns.2008.06.002.

34. Lopez-Gonzalez R, Loza E, Jover JA, Benitez Del Castillo JM, Mendez R, Hernandez-Garcia C, Pato E. Treatment of refractory posterior uveitis with infliximab: a 7-year follow-up study. Scand J Rheumatol. 2009;38(1):58–62. https://doi.org/10.1080/03009740802366076.

35. Herrera-Esparza R, Avalos-Díaz E. Infliximab treatment in a case of rheumatoid scleromalacia perforans. Reumatismo. 2009;61(3):212–5. https://doi.org/10.4081/reumatismo.2009.212.

36. Abalos-Medina GM, Gónzalez-Domínguez J, Ruiz-Villaverde G, Raya-Alvarez E. Infliximab para el tratamiento de la escleritis anterior necrosante asociada a artritis reumatoide seropositiva [Infliximab in the treatment of necrotizing scleritis associated to seropositive rheumatoid arthritis]. Med Clin (Barc). 2010;134(5):235–6. https://doi.org/10.1016/j.medcli.2009.02.009.

37. Kontkanen M, Paimela L, Kaarniranta K. Regression of necrotizing scleritis in Wegener's granulomatosis after infliximab treatment. Acta Ophthalmol. 2010;88(3):e96–7. https://doi.org/10.1111/j.1755-3768.2009.01546.x.

38. Jabbarvand M, Fard MA. Infliximab in a patient with refractory necrotizing scleritis associated with relapsing polychondritis. Ocul Immunol Inflamm. 2010;18(3):216–7. https://doi.org/10.3109/09273941003624914.

39. Oh JY, Kim MK, Wee WR. Infliximab for progressive peripheral ulcerative keratitis in a patient with juvenile rheumatoid arthritis. Jpn J Ophthalmol. 2011;55(1):70–1. https://doi.org/10.1007/s10384-010-0889-7.

40. Hata M, Nakamura T, Sotozono C, Kumagai K, Kinoshita S, Kurimoto Y. Atypical continuous keratitis in a case of rheumatoid arthritis accompanying severe scleritis. Cornea. 2012;31(12):1493–6. https://doi.org/10.1097/ICO.0b013e31826218c7.

41. Khalili S, Mireskandari K. Infliximab for management of severe refractory posterior scleritis in a 9-year-old boy. Can J Ophthalmol. 2020;S0008–4182(20):30835–8. https://doi.org/10.1016/j.jcjo.2020.11.013.

42. Hernandez-Illas M, Tozman E, Fulcher SF, Jundt JW, Davis J, Pflugfelder SC. Recombinant human tumor necrosis factor receptor Fc fusion protein (Etanercept): experience as a therapy for sight-threatening scleritis and sterile corneal ulceration. Eye Contact Lens. 2004;30(1):2–5. https://doi.org/10.1097/01.ICL.0000092064.05514.04.

43. Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and

associated rheumatic disease. Arthritis Rheum. 2001;45(3):252–7. https://doi.org/10.1002/1529-0131(200106)45:3%3c252::AID-ART257%3e3.0.CO;2-5.

44. Galor A, Perez VL, Hammel JP, Lowder CY. Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. Ophthalmology. 2006;113(12):2317–23. https://doi.org/10.1016/j.ophtha.2006.04.038.

45. Tiliakos AN, Tiliakos NA. Ocular inflammatory disease in patients with RA taking etanercept: is discontinuation of etanercept necessary? J Rheumatol. 2003;30(12):2727.

46. Le-Garrec J, Marcelli C, Mouriaux F. Les anti-Tnf peuvent-ils induire des scléro-uvéites? [Can tumor necrosis factor inhibitors induce sclero-uveitis?]. J Fr Ophtalmol. 2009;32(7):511.e1-6. https://doi.org/10.1016/j.jfo.2009.04.029.

47. Gaujoux-Viala C, Giampietro C, Gaujoux T, et al. Scleritis: a paradoxical effect of etanercept? Etanercept-associated inflammatory eye disease. J Rheumatol. 2012;39(2):233–9. https://doi.org/10.3899/jrheum.110865.

48. Sassa Y, Kawano Y, Yamana T, Mashima T, Ishibashi T. A change in treatment from etanercept to infliximab was effective to control scleritis in a patient with rheumatoid arthritis. Acta Ophthalmol. 2012;90(2):e161–2. https://doi.org/10.1111/j.1755-3768.2010.02090.x.

49. Ferguson TA, Griffith TS. The role of Fas ligand and TNF-related apoptosis-inducing ligand (TRAIL) in the ocular immune response. Chem Immunol Allergy. 2007;92:140–54. https://doi.org/10.1159/000099265.

50. Amer R, Levinger N. Psoriasis-associated progressive necrotizing posterior scleritis: a 6-year follow-up. Eur J Ophthalmol. 2020;30(3):NP7–10. https://doi.org/10.1177/1120672118823121.

51. Dutta-Majumder P, Jayshree G, David RL, Kaushik V. A case of idiopathic necrotizing scleritis with secondary glaucoma treated successfully with golimumab and Ahmed valve implantation. Indian J Ophthalmol. 2019;67(8):1360–1362. https://doi.org/10.4103/ijo.IJO_2081_18.

52. Tlucek PS, Stone DU. Certolizumab pegol therapy for rheumatoid arthritis-associated scleritis. Cornea. 2012;31(1):90–1. https://doi.org/10.1097/ICO.0b013e318211400a.

53. Cheung CM, Murray PI, Savage CO. Successful treatment of Wegener's granulomatosis associated scleritis with rituximab. Br J Ophthalmol. 2005;89(11):1542. https://doi.org/10.1136/bjo.2005.075689.

54. Ahmadi-Simab K, Lamprecht P, Nölle B, Ai M, Gross WL. Successful treatment of refractory anterior scleritis in primary Sjogren's syndrome with rituximab. Ann Rheum Dis. 2005;64(7):1087–8. https://doi.org/10.1136/ard.2004.027128.

55. Joshi L, Tanna A, McAdoo SP, et al. Long-term outcomes of rituximab therapy in ocular granulomatosis with polyangiitis: impact on localized and nonlocalized disease. Ophthalmology. 2015;122(6):1262–8. https://doi.org/10.1016/j.ophtha.2015.01.016.

56. Ahmed A, Foster CS. Cyclophosphamide or rituximab treatment of scleritis and uveitis for patients with granulomatosis with polyangiitis. Ophthalmic Res. 2019;61(1):44–50. https://doi.org/10.1159/000486791.

57. Recillas-Gispert C, Serna-Ojeda JC, Flores-Suárez LF. Rituximab in the treatment of refractory scleritis in patients with granulomatosis with polyangiitis (Wegener's). Graefes Arch Clin Exp Ophthalmol. 2015;253(12):2279–84. https://doi.org/10.1007/s00417-015-3198-5.

58. You C, Ma L, Lasave AF, Foster CS. Rituximab induction and maintenance treatment in patients with scleritis and granulomatosis with polyangiitis (Wegener's). Ocul Immunol Inflamm. 2018;26(8):1166–73. https://doi.org/10.1080/09273948.2017.1327602.

59. Morarji J, Joshi L, Tomkins-Netzer O, Lightman S, Taylor SR. Combined infliximab and rituximab in necrotising scleritis. Case Rep Ophthalmol. 2012;3(3):286–90. https://doi.org/10.1159/000342842.

60. Stilling-Vinther MK, Pedersen BS. Fatal Pneumocystis jirovecii pneumonia following immunosuppressive therapy with rituximab and prednisolone for posterior scleritis. Acta Ophthalmol. 2012;90(2):e154–5. https://doi.org/10.1111/j.1755-3768.2011.02127.x.

61. Bussone G, Kaswin G, de Menthon M, Delair E, Brézin AP, Guillevin L. Macular oedema following rituximab infusion in two patients with Wegener's granulomatosis. Clin Exp Rheumatol. 2010;28(1 Suppl 57):90–2.

62. Chauhan S, Kamal A, Thompson RN, Estrach C, Moots RJ. Rituximab for treatment of scleritis associated with rheumatoid arthritis. Br J Ophthalmol. 2009;93(7):984–5. https://doi.org/10.1136/bjo.2008.147157.

63. Onal S, Kazokoglu H, Koc A, Yavuz S. Rituximab for remission induction in a patient with relapsing necrotizing scleritis associated with limited Wegener's granulomatosis. Ocul Immunol Inflamm. 2008;16(5):230–2. https://doi.org/10.1080/09273940802331643.

64. Kurz PA, Suhler EB, Choi D, Rosenbaum JT. Rituximab for treatment of ocular inflammatory disease: a series of four cases. Br J Ophthalmol. 2009;93(4):546–8. https://doi.org/10.1136/bjo.2007.133173.

65. Taylor SR, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. Arthritis Rheum. 2009;60(5):1540–7. https://doi.org/10.1002/art.24454.

66. Iaccheri B, Androudi S, Bocci EB, Gerli R, Cagini C, Fiore T. Rituximab treatment for persistent scleritis associated with rheumatoid arthritis. Ocul Immunol Inflamm. 2010;18(3):223–5. https://doi.org/10.3109/09273941003739928.

67. Bogdanic-Werner K, Fernandez-Sanz G, Alejandre Alba N, Ferrer Soldevila P, Romero-Bueno FI, Sanchez-Pernaute O. Rituximab therapy for refractory idiopathic scleritis. Ocul Immunol Inflamm. 2013;21(4):329–32. https://doi.org/10.3109/09273948.2013.788724.

68. Kasi SK, Kim HJ, Basham RP, et al. Idiopathic orbital inflammation associated with necrotizing scleritis and temporal bone inflammation. Ophthalmic Plast Reconstr Surg. 2016;32(4):e77–9. https://doi.org/10.1097/IOP.0000000000000251.

69. Hardy S, Hashemi K, Catanese M, et al. Necrotising scleritis and peripheral ulcerative keratitis associated with rheumatoid arthritis treated with rituximab. Klin Monbl Augenheilkd. 2017;234(4):567–570. https://doi.org/10.1055/s-0042-121315.

70. Fujita Y, Fukui S, Endo Y, et al. Peripheral ulcerative keratitis associated with granulomatosis with polyangiitis emerging despite cyclophosphamide, successfully treated with rituximab. Intern Med. 2018;57(12):1783–8. https://doi.org/10.2169/internalmedicine.0215-17.

71. Pérez-Jacoiste Asín MA, Charles P, Rothschild PR, et al. Ocular involvement in granulomatosis with polyangiitis: a single-center cohort study on 63 patients. Autoimmun Rev. 2019;18(5):493–500. https://doi.org/10.1016/j.autrev.2019.03.001.

72. Murthy SI, Shah S, Bagga B, Dudam R. Rituximab therapy combined with methotrexate for severe necrotizing scleritis in a case of granulomatosis with polyangiitis. Indian J Ophthalmol. 2020;68(9):1981–3. https://doi.org/10.4103/ijo.IJO_2249_19.

73. Caso F, Fiocco U, Costa L, Sfriso P, Punzi L, Doria A. Successful use of rituximab in a young patient with immunoglobulin G4-related disease and refractory scleritis. Joint Bone Spine. 2014;81(2):190–2. https://doi.org/10.1016/j.jbspin.2013.07.011.

74. Soon AK, Chan TY. An atypical case of bilateral posterior scleritis in a patient with chronic lymphocytic leukemia. Can J Ophthalmol. 2015;50(4):e60–3. https://doi.org/10.1016/j.jcjo.2015.05.009.

75. Xu C, Ricciuti A, Caturegli P, Keene CD, Kargi AY. Autoimmune lymphocytic hypophysitis in association with autoimmune eye disease and sequential treatment with infliximab and rituximab. Pituitary. 2015;18(4):441–7. https://doi.org/10.1007/s11102-014-0592-7.

76. Fidelix TS, Vieira LA, Trevisani VF. Management of necrotizing scleritis after pterygium surgery with rituximab. Arq Bras Oftalmol. 2016;79(5):339–41. https://doi.org/10.5935/0004-2749.20160097.

77. Fabiani C, Sota J, Tosi GM, et al. The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases. Clin Rheumatol. 2017;36(10):2307–18. https://doi.org/10.1007/s10067-016-3527-z.

78. Botsios C, Sfriso P, Ostuni PA, Todesco S, Punzi L. Efficacy of the IL-1 receptor antagonist, anakinra, for the treatment of diffuse anterior scleritis in rheumatoid arthritis. Report of two cases. Rheumatol (Oxford). 2007;46(6):1042–3. https://doi.org/10.1093/rheumatology/kem052.

79. Fabiani C, Sota J, Sainz-de-la-Maza M, et al. New potential weapons for refractory scleritis in the era of targeted therapy. Mediators Inflamm. 2020;2020:8294560. https://doi.org/10.1155/2020/8294560.

80. Lopalco G, Fabiani C, Sota J, et al. IL-6 blockade in the management of non-infectious uveitis. Clin Rheumatol. 2017;36(7):1459–69. https://doi.org/10.1007/s10067-017-3672-z.

81. Tode J, Zeuner R, Saeger M, Roider J, Nölle B. Tocilizumab and steroid boli for treatment-resistant anterior necrotizing scleritis. Acta Ophthalmol. 2015;93(8):e683–4. https://doi.org/10.1111/aos.12720.

82. Silpa-Archa S, Oray M, Preble JM, Foster CS. Outcome of tocilizumab treatment in refractory ocular inflammatory diseases. Acta Ophthalmol. 2016;94(6):e400–6. https://doi.org/10.1111/aos.13015.

83. Poelman HJ, Van Daele PLA, Rothova A. Successful tocilizumab treatment for scleritis. Ocul Immunol Inflamm. 2020;28(2):285–7. https://doi.org/10.1080/09273948.2019.1617885.

84. Farhat R, Clavel G, Villeneuve D, et al. Sustained remission with tocilizumab in refractory relapsing polychondritis with ocular involvement: a case series. Ocul Immunol Inflamm. 2021;29(1):9–13. https://doi.org/10.1080/09273948.2020.1763405.

85. Shimizu H, Nishioka H. Successful treatment with tocilizumab for refractory scleritis associated with relapsing polychondritis. Scand J Rheumatol. 2017;46(5):418–9. https://doi.org/10.1080/03009742.2016.1275774.

86. Michael E, Lange EL, Guest S. Paradoxical nodular scleritis during tocilizumab therapy: a case report. J Rheumatol. 2017;44(11):1760–1. https://doi.org/10.3899/jrheum.170234.

87. Dominguez-Casas LC, Sánchez-Bilbao L, Calvo-Río V, et al. Biologic therapy in severe and refractory peripheral ulcerative keratitis (PUK). Multicenter study of 34 patients. Semin Arthritis Rheum. 2020;50(4):608–615. https://doi.org/10.1016/j.semarthrit.2020.03.023.

88. Birolo C, Zannin ME, Arsenyeva S, et al. Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. J Rheumatol. 2016;43(11):2068–73. https://doi.org/10.3899/jrheum.151389.

89. Matsumoto S, Matsumoto K, Takaya H, Otake H, Mashima H. Efficacy of ustekinumab against spondyloarthritis associated with Crohn's disease: a case report and review of the literature. Open Access Rheumatol. 2020;12:133–7. https://doi.org/10.2147/OARRR.S263259.

90. Papaliodis GN, Chu D, Foster CS. Treatment of ocular inflammatory disorders with daclizumab. Ophthalmology. 2003;110(4):786–9. https://doi.org/10.1016/S0161-6420(02)01932-2.

91. Kommaraju KR, Moroi S, Demirci H. Diffuse anterior scleritis and secondary glaucoma as a manifestation of adult T-cell prolymphocytic leukemia. Cornea. 2014;33(8):873–4. https://doi.org/10.1097/ICO.0000000000000180.

92. Hodge JA, Kawabata TT, Krishnaswami S, et al. The mechanism of action of tofacitinib—an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2016;34(2):318–28.

93. Paley MA, Karacal H, Rao PK, Margolis TP, Miner JJ. Tofacitinib for refractory uveitis and scleritis. Am J Ophthalmol Case Rep. 2018;13:53–5. https://doi.org/10.1016/j.ajoc.2018.12.001.

94. Pyare R, Kaushik V, Dutta Majumder P, Biswas J. Tofacitinib in recalcitrant scleritis: first case report from India. Indian J Ophthalmol. 2020;68(9):1988–90. https://doi.org/10.4103/ijo.IJO_534_20.

95. Vergouwen DPC, Rothova A, Berge JCT, et al. Current insights in the pathogenesis of scleritis. Exp Eye Res. 2020;197: 108078. https://doi.org/10.1016/j.exer.2020.108078.

96. Riono WP, Hidayat AA, Rao NA. Scleritis: a clinicopathologic study of 55 cases. Ophthalmology. 1999;106(7):1328–33. https://doi.org/10.1016/S0161-6420(99)00719-8.

97. Berkenstock MK, Carey AR. Health system wide "big data" analysis of rheumatologic conditions and scleritis. BMC Ophthalmol. 2021;21(1):14. https://doi.org/10.1186/s12886-020-01769-3.

98. Yoshida A, Watanabe M, Okubo A, Kawashima H. Clinical characteristics of scleritis patients with emphasized comparison of associated systemic diseases (anti-neutrophil cytoplasmic antibody-associated vasculitis and rheumatoid arthritis). Jpn J Ophthalmol. 2019;63(5):417–24. https://doi.org/10.1007/s10384-019-00674-7.