Management of noninfectious scleritis

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Abstract: Scleritis is a manifestation of inflammatory eye disease that involves the sclera. It can be divided into multiple subtypes, including diffuse anterior, nodular anterior, necrotizing, and posterior scleritis. In many cases, scleritis is restricted to the eye; however, it can occur in the context of systemic illness, particularly autoimmune and infectious conditions. Patients with autoimmune conditions, such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and polyangiitis with granulomatosis, may develop scleritis flares that may require topical and systemic therapy. Initial therapy typically involves oral nonsteroidal anti-inflammatory drugs (NSAIDs); however, it is important to address the underlying condition, particularly if systemic. Other treatment regimens typically involve either local or systemic steroids or the use of immunomodulatory agents, which have a wide range of efficacy and documented use in the literature. There is a myriad of immunomodulatory agents used in the treatment of scleritis including antimetabolites, calcineurin inhibitors, biologics, and alkylation agents. In this review, we highlight the various subtypes of noninfectious scleritis and explore each of the mainstay agents used in the management of this entity. We explore the use of steroids and NSAIDs in detail and discuss evidence for various immunomodulatory agents.

Keywords: alkylation agents, antimetabolites, biologics, calcineurin inhibitors, corticosteroids, immunomodulators, inflammatory eye disease, NSAIDs, ocular inflammatory disease, scleritis, TNF-α inhibitors

Introduction

Scleritis is a relatively uncommon, highly symptomatic inflammatory disease of the sclera. It is typically divided into diffuse anterior, nodular anterior, necrotizing, and posterior subtypes.1 In most cases, the disease is restricted to the eye; however, in an estimated 20–50% of patients, it may be associated with a systemic inflammatory condition.2–6 Rheumatoid arthritis is particularly prevalent among patients with scleritis; other autoimmune conditions, such as granulomatosis with polyangiitis, relapsing polychondritis, systemic lupus erythematosus, inflammatory bowel disease, seronegative polyarthropathies, Sjögren’s syndrome, and polyarteritis nodosa, are also associated with scleritis.2,3,6–8 In rare cases, it may be associated with localized infection, such as herpes simplex, varicella zoster, acanthamoeba, bacterial, or fungal infections, or other systemic infectious etiologies such as syphilis or tuberculosis.9,10

Scleritis can be refractory to treatment and can cause vision-threatening complications including severe thinning of the sclera and globe perforation if left untreated.

Numerous treatment options are available for acute scleritis. Initial therapy often includes oral nonsteroidal anti-inflammatory drugs (NSAIDs).11,12 A variety of NSAIDs have been used for scleritis (e.g. indomethacin, ibuprofen, naproxen, and flurbiprofen). When patients are refractory to NSAIDs, corticosteroids can be administered topically, systematically, or via local sub-Tenon’s injection. If the response is not adequate, then therapy can be escalated to include immunomodulatory agents including calcineurin inhibitors (e.g. cyclosporine and tacrolimus), antimetabolites (e.g. methotrexate, azathioprine, and mycophenolate), alkylation agents (e.g. cyclophosphamide and chlorambucil), and biologics (e.g. infliximab, adalimumab,
certolizumab, and rituximab). Immunomodulatory agents are also used to decrease patients’ exposure to corticosteroids. The evidence supporting these treatments is variable, ranging from randomized clinical trials (e.g. for rituximab) to sporadic case reports (e.g. for adalimumab and certolizumab). Here, we review the literature on the management of noninfectious scleritis.

**Patient factors and outcomes**
Numerous patient factors have been noted to affect treatment outcomes in patients with scleritis. For example, patients who have scleritis in the context of systemic disease were more likely to require more aggressive treatment. Another series found that patients with systemic disease were also significantly more likely to have visual decline than patients with idiopathic scleritis. Lavric et al. noted that Crohn’s disease was associated with an increased risk of recurrence of scleritis in patients with posterior scleritis. Another study found that patients with relapsing polychondritis were more likely than those with idiopathic scleritis to have necrotizing scleritis, recurrence of scleritis, and decreased vision when compared with patients with other autoimmune diseases. In one study, smokers were found to take an average of 1 month longer to respond to therapy than nonsmokers. Other factors, such as female gender, have been associated with increased rates of scleritis but have not been associated with disease severity or treatment response.

**Treatment utilization**
A small number of studies have characterized the utilization of the types of treatments used for scleritis. For example, in a retrospective study of 128 patients with episcleritis and scleritis, including 93 with scleritis, 28.9% were treated with topical corticosteroids alone, 1.1% were treated with either topical or oral NSAIDs, 58.1% received oral corticosteroids, and 15% were treated with a noncorticosteroid systemic immunosuppressive drug. The prevalence of the usage of specific immunosuppressive drugs was not reported in this study.

Other studies have included some data on the use of specific immunosuppressive drugs. For example, in one retrospective study of 134 scleritis patients, of whom 69 had treatment information available, 30% of the patients with scleritis required oral NSAIDs, 31.9% required oral corticosteroids, and 26.1% required noncorticosteroid systemic immunosuppressive drugs. The authors reported that cyclophosphamide was the most commonly used nonsteroidal agent. In a study of 123 Japanese patients with scleritis, 35% of patients received topical corticosteroids, 15.4% received an injection of triamcinolone acetonide, 23.6% received oral NSAIDs, and 52.8% received systemic immunosuppressive medications. The most common of these was systemic corticosteroids in 45.5% of patients, followed by methotrexate in 11.4% of patients. Notably, neither of these studies included patients on biologic therapies and the authors did not attempt to assess the efficacy of the treatments used.

Lavric et al. did attempt to assess the efficacy of different therapies. In their study of 114 patients with posterior scleritis, 48.2% received topical steroids, 38.6% received oral systemic steroids, 8.8% received intravenous steroids, 4% received periocular steroid injections, 34.2% received systemic NSAIDs, and 32.5% received systemic noncorticosteroid immunosuppressive medications. The most commonly used noncorticosteroid immunosuppressive medication was azathioprine (17.5% of patients), followed by mycophenolate (7.0% of patients). The authors’ assessment of mycophenolate found that patients on mycophenolate stayed resolved from a scleritis flare for a longer period of time. Of note, the authors did not assess the efficacy of biologics because only a small number (<5%) of patients received any biologic agent.

**NSAIDs and steroids**
Scleritis is a fairly uncommon disorder; therefore, there are limited large series or randomized clinical trials characterizing the types of scleritis or the efficacy of different treatments. Many therapies are used in the management of scleritis including oral NSAIDs, topical steroids, topical NSAIDs in select cases, locally injected corticosteroids, systemic corticosteroids, and noncorticosteroid immunomodulatory therapies. Tappeiner et al. proposed a stepwise approach to management that started with systemic NSAIDs, followed by systemic corticosteroids, and then noncorticosteroid systemic immunomodulatory agents. They did not recommend the use of topical corticosteroids as monotherapy. Foster et al. proposed a similar ‘step-ladder’ approach for ocular inflammation, also starting with oral NSAIDs, followed by systemic corticosteroids,
with noncorticosteroid agents added 2–3 months later to decrease patients’ exposure to corticosteroids and their risk of systemic side effects.

Systemic NSAIDs and systemic steroids are the mainstay of treatment for acute scleritis and have shown to be efficacious in multiple studies. Watson and Hayreh\(^1\) demonstrated the efficacy of NSAIDs and corticosteroids and recommended indomethacin as a first-line treatment. McCluskey and Wakefield\(^2\) also demonstrated the efficacy of corticosteroids for the treatment of scleritis. All 14 patients in their cohort demonstrated improvement on pulsed methylprednisolone, though 6 (43%) required additional immunosuppression to achieve quiescence. In a large retrospective study of 392 patients with non-necrotizing anterior scleritis, Sainz de la Maza et al.\(^2\) demonstrated a 36.7% response rate to oral NSAIDs, which included indomethacin, diflunisal, naproxen, ibuprofen, piroxicam, diclofenac, meloxicam, and celecoxib. The successful response to treatment with NSAIDs in idiopathic diffuse or nodular anterior scleritis was associated with a low degree of inflammation, idiopathic disease, and no ocular complications. Among those on systemic corticosteroids, 7.4% had a successful resolution of symptoms. Patients with a high degree of inflammation and idiopathic diffuse or nodular scleritis were more likely to experience resolution of their scleritis on corticosteroids compared with systemic NSAIDs. Those patients with bilateral scleritis, anterior necrotizing scleritis, and associated systemic disease required the addition or substitution of systemic immunomodulatory therapy to steroid therapy. In patients with a low degree of inflammation, the authors recommended using NSAIDs as first-line therapy if there are no contraindications, and further recommended trialing a second NSAID if the scleritis is refractory to the first NSAID. They recommended using corticosteroids as first-line therapy in patients with a greater degree of inflammation. Jabs et al.\(^1\) demonstrated that 30% of patients with scleritis responded to NSAIDs when initiated on indomethacin 25 mg four times a day, and that 50% of those with nodular anterior scleritis responded to systemic corticosteroids. They also recommended NSAIDs, specifically indomethacin, as a first-line agent, but cautioned that patients with posterior scleritis or necrotizing scleritis may require systemic corticosteroids. Agrawal et al.\(^2\) demonstrated the efficacy of flurbiprofen; however, the authors reported that it was much less effective in patients with systemic autoimmune disease. While patients with posterior scleritis are usually treated with corticosteroids, one small series demonstrated the efficacy of indomethacin in posterior scleritis.\(^2\)

Most of these studies have looked at the efficacy of NSAIDs as a group and at nonselective NSAIDs. Bauer et al.\(^2\) assessed the efficacy of the selective COX-2 inhibitor celecoxib in the treatment of scleritis. Of the 24 patients in their cohort, 22 demonstrated clinical improvement. The authors recommended celecoxib as a treatment because of the lower rate of gastrointestinal complications. Due to the demonstrated efficacy of NSAIDs for scleritis and the relatively benign side-effect profile, oral NSAIDs are overall considered as first-line therapy. However, systemic corticosteroids may be used as a first-line treatment in patients with contraindications to NSAID use (e.g. renal disease and peptic ulcer disease), intolerable side effects or allergies to NSAIDs, necrotizing or posterior scleritis, and a high degree of inflammation.

Topical steroids have also been used in the management of scleritis. A phase I/II clinical trial of 32 patients was conducted to assess the efficacy of topical 1% prednisolone acetate. Of those who received topical steroids, 47% had successful resolution of inflammation. The authors proposed using topical steroids as a first-line treatment to spare patients the side effects of systemic NSAIDs and steroids. However, others have not considered topical steroids as monotherapy for scleritis although it may be useful in episcleritis.\(^1\),\(^2\) Agrawal et al.\(^2\) found no difference in the progression of disease in patients on combination NSAID and topical corticosteroid therapy when compared with NSAID therapy alone, but proposed that it could help with pain modulation.

Topical NSAIDs have been used with some success in episcleritis; however, no studies have looked at topical NSAIDs specifically for scleritis. Topical NSAIDs are not recommended in the treatment of acute scleritis due to the risk of scleral melt.\(^2\),\(^3\)

Oral corticosteroid therapy has been a mainstay of scleritis therapy, but recent data demonstrate efficacy for subconjunctival and sub-Tenon’s steroid injection among patients with local, non-infectious, and non-necrotizing scleritis. In one study of 68 eyes receiving up to 40 mg of subconjunctival triamcinolone acetonide, there was a
97% response rate with 67% of patients remaining in remission after 24 months. In another retrospective study of 38 eyes, 36 eyes had resolution within 6 weeks of injection.

**Immunomodulatory agents**

Immunomodulatory therapy (IMT) is utilized in patients who are refractory to systemic NSAIDs and corticosteroids, as a method to taper patients off of chronic steroids, as an option for long-term management of ocular inflammation, or to manage an underlying systemic disease. One study showed that 38% of patients with scleritis required escalation to IMT. In another study, 25% of patients with scleritis required escalation to IMT. Those with necrotizing scleritis were more likely to require IMT, with 70% of these patients requiring systemic immunomodulation for adequate scleritis control. These studies measured the prevalence of the usage of IMT but did not assess the efficacy of any agents. Other studies have assessed the individual efficacies of the most commonly used agents. The largest of these studies is the systemic immunosuppressive therapy for eye disease (SITE) study, which is a retrospective cohort study that evaluated the efficacy of several treatments for inflammatory eye diseases, including scleritis.

**Antimetabolites**

Methotrexate is an antimetabolite agent that inhibits folate metabolism. The largest study evaluating its efficacy was a SITE study that included 384 patients (639 eyes) with inflammatory eye disease. This included 56 patients (84 eyes) with scleritis. In their cohort, 38.6% of patients with scleritis treated with methotrexate at a median dose of 12.5 mg/week as a single adjunct to systemic corticosteroid treatment achieved absence of symptoms within 6 months of treatment, and 37.3% achieved steroid-sparing treatment success, defined as quiescence at a dose equivalent to 10 mg or less of prednisone, within 6 months. Other smaller retrospective studies, as well as case reports and case series, have reported successful treatment of scleritis with mycophenolate mofetil. In one such study of four patients with scleritis on mycophenolate, three patients were able to decrease their steroid dose. In another study of 22 patients on mycophenolate, which included 20 patients who had failed another immunomodulatory agent, all patients achieved resolution of inflammation and were able to decrease the dose of corticosteroids to a mean daily dose of 5.8 mg. A case series of five patients with vasculitis-associated inflammatory eye disease, including one with scleritis, reported treatment success of a patient with scleritis. Enteric-coated mycophenolate was demonstrated to be efficacious at controlling symptoms in a retrospective review of five patients.

Other smaller studies have demonstrated the efficacy of mycophenolate specifically as a steroid-sparing agent. A study of 84 patients with inflammatory eye disease treated with mycophenolate, of whom 17% had scleritis, found that 82% of patients had steroid-sparing resolution of symptoms. The median time to steroid-sparing resolution was 3.5 months. Another retrospective study of 10 patients with inflammatory eye disease treated with mycophenolate, including three with scleritis, found that steroid-sparing resolution was achieved in all patients and that the average number of relapses decreased from 3.1 per patient per year to 0.8 per patient per year \((p < 0.005)\). In a study of four patients with active scleritis in which mycophenolate was added...
as adjunctive therapy to cyclosporine or methotrexate, mycophenolate was not found to be effective. This study also included four patients with inactive scleritis on steroids who were given mycophenolate as a steroid-sparing agent. The steroid dose was tapered by 50% in three of these patients. The authors concluded that mycophenolate may be effective as a steroid-sparing agent, but not as an adjunctive immunosuppressant in active disease.43

Other studies have demonstrated a negative effect of treatment with mycophenolate, including lower rates of resolution of inflammation and increased likelihood of relapse. One of these studies included 85 patients with inflammatory eye disease, including seven with scleritis, who had previously failed methotrexate. Of those who received mycophenolate, 55% of patients achieved remission and were able to be taken off the medication. However, the authors also found that treatment with mycophenolate was negatively associated with resolution of inflammation [odds ratio (OR) = 0.19; 95% confidence interval (CI) = 0.04–0.93; \( p = 0.04 \)].44 Another study had a similar finding. In this study of 114 patients with posterior scleritis, mycophenolate was associated with accelerated time to relapse in a Cox proportional hazards model.20 The authors speculated that patients with more severe scleritis are placed on mycophenolate, which may result in the observed paradoxical effect; however, they also discuss that mycophenolate has been associated with an increased risk of recurrence in other autoimmune disorders including lupus nephritis and immunoglobulin A (IgA) nephropathy.45–47 Studies evaluating mycophenolate use in scleritis have had mixed results, with some demonstrating its efficacy in the resolution of scleritis, a steroid-sparing benefit, or a negative effect. Overall, most studies have reported a positive effect of mycophenolate treatment.

Azathioprine is an antimetabolite prodrug of 6-mercaptopurine that inhibits B and T lymphocytes by inhibiting purine metabolism.14 In a SITE study of patients with scleritis treated with azathioprine as an adjunct to corticosteroids, 20% were controlled within 6 months, and 47.8% of patients with inflammatory eye disease (not stratified for scleritis) were successfully weaned to less than 10 mg of prednisone within 6 months.48 Though less studied than methotrexate or mycophenolate moфetil, successful azathioprine use has been reported in multiple other studies, including in cases of necrotizing scleritis, posterior scleritis, and vasculitis-associated scleritis.21,23,49,50

Calcineurin inhibitors
Calcineurin inhibitors function by inhibiting the transcription of interleukin-2 in T lymphocytes, which decreases T-cell activation. They are most commonly used in scleritis associated with granulomatosis with polyangiitis.12 Cyclosporine A is one such calcineurin inhibitor.14 The efficacy of systemic cyclosporine was first reported in a 1989 case series in which five out of seven corticosteroid-refractory scleritis patients had a resolution of symptoms when treated with cyclosporine.51 In another early study of five patients, all five were successfully able to reduce corticosteroid dose upon initiation of cyclosporine.52 In a case series of two patients with idiopathic scleritis, both corticosteroid-refractory patients had a resolution of symptoms on systemic cyclosporine.53 Another series of six patients with necrotizing scleritis were also successfully treated with cyclosporine.54 In a SITE study including 373 patients being treated with cyclosporine A, 52.8% achieved remission within 6 months.55 This was the largest study evaluating the use of cyclosporine A in scleritis patients, though only 4% of patients in the study (15 patients) had scleritis. The successful use of topical cyclosporine for scleritis has also been reported.56

Tacrolimus, another calcineurin inhibitor, has been reported to be successfully used in the treatment of scleritis in both systemic and topical forms.57–59 Subconjunctival injections of sirolimus, another calcineurin inhibitor, have been reported to be successful in a small phase I/II clinical trial of five patients with necrotizing scleritis.60

Alkylating agents
Alkylating agents, including cyclophosphamide, exert a cytotoxic effect on B and T cells by crosslinking DNA bases. Few studies have assessed the efficacy of these treatments in scleritis patients. One large retrospective series of 215 patients with ocular inflammatory diseases, including 22.3% with scleritis, reported that 30% of patients with scleritis treated with cyclophosphamide were able to be weaned to low-dose steroids within 6 months and 60.5% within 12 months.61 In another study of 16 patients with corticosteroid-refractory necrotizing scleritis or
peripheral ulcerative keratitis associated with rheumatoid arthritis, cyclophosphamide and methotrexate were the most effective treatments.62

**Biologics**

Biologics have also been studied for the management of scleritis. The most commonly used biologics for scleritis are tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) inhibitors, including the monoclonal antibodies adalimumab, infliximab, and certolizumab, and the soluble TNF receptor fusion protein etanercept, and the CD20 inhibitor rituximab. A systematic review of published studies investigating the use of biologics in scleritis patients was conducted in 2015.63 At that time, there were no clinical trials for biologic use for the treatment of scleritis. There were 30 case reports and case series encompassing 80 patients who were treated with a biologic agent. The biologic agent with the most reports was the TNF-\(\alpha\) inhibitor, infliximab, an agent that has successfully been used in other autoimmune diseases and has been FDA (US Food and Drug Administration) approved for rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis.64 The use of infliximab in the treatment of scleritis was reported in 18 studies encompassing 47 patients. Of those cases, 14 were idiopathic, 14 were associated with rheumatoid arthritis, and 19 were associated with inflammatory diseases other than rheumatoid arthritis. Among the patients on infliximab therapy, 96% had an improvement in visual acuity or inflammation, 64% were able to reduce or discontinue corticosteroids, and 36% were able to discontinue infliximab.

Adalimumab, another TNF-\(\alpha\) inhibitor, is FDA approved for juvenile inflammatory arthritis, rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, and plaque psoriasis.84 It is also approved for the treatment of noninfectious intermediate, posterior, and panuveitis in children above the age of 2 years and adults. Two cases of adalimumab use in scleritis were reported, one in a patient with psoriasis and one with rheumatoid arthritis. Both had resolution of inflammation.65,66 Certolizumab is a PEGylated TNF-\(\alpha\) inhibitor. PEGylation increases the half-life and decreases the immunogenicity of certolizumab.67 One reported case of a patient on certolizumab had successful resolution.17 Etanercept is a soluble TNF receptor fusion protein, unlike the other TNF-\(\alpha\) inhibitors, which are monoclonal antibodies. It is FDA approved for rheumatoid arthritis, polyarticular JIA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis.64 In one study encompassing six patients with rheumatoid arthritis-associated scleritis on etanercept, three of the patients failed to respond, and the other three had a recurrence of ocular symptoms while on therapy. Etanercept was not effective in the control of scleritis; however, it was effective in controlling the underlying rheumatoid arthritis symptoms.68

Rituximab is a chimeric anti-CD20 monoclonal antibody. The use of rituximab in the treatment of scleritis was reported in 10 studies encompassing 26 scleritis patients treated with rituximab. This included 11 patients with vasculitis. All reported improvement in scleritis symptoms. A phase I/II trial of rituximab found it effective in 9 out of 12 patients.15 The authors of this review concluded that infliximab and adalimumab may be superior to etanercept, and that rituximab may be preferable for vasculitis-associated scleritis. A retrospective study that was not included in this review included 17 patients (26 eyes) with scleritis treated with infliximab, adalimumab, or both at separate times. Of these, 15 patients (88%) achieved resolution of symptoms for 2 months or more.69

Since the release of this 2015 review, a number of other studies and case reports have been published on the use of biologics in the treatment of scleritis. One SITE study included 32 patients with inflammatory eye disease treated with adalimumab, including 9 patients with scleritis.70 Of the 15 patients with active ocular inflammation at 6 months, 7 (47%) had a resolution of symptoms. A case series reported two patients with necrotizing scleritis successfully treated with adalimumab. One of these patients had a resolution on adalimumab and methotrexate after failing mycophenolate and tacrolimus; the other resolved on adalimumab after failing methotrexate.71 A case of Takayasu arteritis–associated scleritis was also reported to be treated successfully with adalimumab.72 A prospective cohort study followed 43 patients with uveitis or scleritis on adalimumab or infliximab for more than 1 year. Resolution of symptoms was achieved in 91% of patients, with a median resolution time of 1.2 years. An adverse event was reported in 54% of patients, and 9% had a serious adverse event requiring cessation of therapy.73
Several more recent studies report the efficacy of rituximab in scleritis use, especially in vasculitis-associated scleritis and necrotizing scleritis. In a study of 37 patients with granulomatosis with polyangiitis-associated eye disease, including 20 patients with scleritis, 86% had resolution of ocular symptoms in 6 months. In a series of 9 patients (12 eyes) with granulomatosis with polyangiitis-associated scleritis, all patients achieved quiescence on rituximab. All patients had previously failed corticosteroids and another IMT. In another retrospective study of 15 patients, 14 had a treatment response to rituximab, including 6 patients with granulomatosis with polyangiitis. In another study that included 8 patients (12 eyes) with granulomatosis with polyangiitis-associated necrotizing scleritis, all patients had an improvement of symptoms and 7 patients had resolution of symptoms. In a case series of three patients with peripheral ulcerative keratitis, including two with concurrent necrotizing scleritis, two patients received rituximab and had a positive treatment response. A case report of necrotizing scleritis after pterygium surgery also reported successful treatment on rituximab after the failure of corticosteroids, azathioprine, and cyclophosphamide.

Other less commonly used biologics have been reported to be used in scleritis patients. Tocilizumab is a monoclonal antibody that targets the interleukin-6 receptor, which inhibits interleukin-6-mediated lymphocyte activation. Only one case report exhibited success in treating a patient with giant cell arteritis-associated scleritis with tocilizumab. Anakinra is a biologic agent that inhibits the interleukin-1 receptor. One pilot study evaluated the efficacy of anakinra in refractory scleritis in 10 patients. Nine of the patients had complete quiescence of symptoms.

Numerous studies have demonstrated the efficacy of biologics for the treatment of scleritis; however, there have been reports of worsening inflammatory eye disease that appears to be paradoxically associated with biologic use. Particularly, etanercept has been implicated in these studies. A case series by Gaojoux-Viala et al. discussed three rheumatoid arthritis patients who developed scleritis associated with the administration of etanercept. Each of these patients had resolution of ocular inflammation upon discontinuation of etanercept. The authors also conducted a systematic review and found 42 cases of inflammatory eye disease associated with the use of etanercept, including 8 with scleritis. In 28 patients, withdrawal of etanercept resulted in resolution of symptoms, and in 6 cases symptoms were exacerbated upon rechallenge with etanercept. Though more commonly associated with etanercept, there have also been reports of inflammatory eye disease associated with infliximab. A review reported 22 cases of infliximab-associated uveitis in the literature. There were no cases of infliximab-associated scleritis.

Comparison of IMTs
Most studies have only assessed the efficacy of one IMT, making it difficult to compare the efficacy of treatment options. Few studies have made head-to-head comparisons of the efficacy of different treatments or treatment classes. A recent retrospective study looking at the SITE cohort compared the outcomes in patients treated with methotrexate and those treated with mycophenolate. It included 352 patients with inflammatory eye disease, including 59 with scleritis. Survival analysis demonstrated a shorter time to treatment success in patients on mycophenolate when compared with methotrexate. Rates of success converged at the 9-month timepoint. Prior to 9 months, a higher proportion of patients on mycophenolate had successful resolution. A retrospective cohort of 257 patients with inflammatory eye disease, of whom 23% had scleritis, compared the efficacy of methotrexate, mycophenolate, and azathioprine. The authors found that the median time to treatment success was 4 months for mycophenolate, 4.8 for azathioprine, and 6.5 months for methotrexate. They concluded that mycophenolate controls inflammation in a shorter time than the other agents. In this cohort, patients on azathioprine were more likely to have side effects, and discontinue treatment due to side effects, compared with those on methotrexate or mycophenolate.

A retrospective cohort study of 50 patients compared patients on cyclophosphamide against a pooled group of patients on other IMTs (methotrexate, mycophenolate, azathioprine, and cyclosporine). They found no significant difference between cyclophosphamide and other agents in terms of remission rate, relapse rate, steroid-sparing, or visual loss, but patients on cyclophosphamide were more likely to develop leukopenia and hemorrhagic cystitis and discontinue medication due to side effects.
Conclusion

Scleritis is a potentially vision-threatening inflammatory condition involving the deep episclera and sclera. Noninfectious forms of scleritis can be idiopathic or associated with an underlying autoimmune or rheumatologic process. Oral NSAIDs are typically the first-line agent for the treatment of scleritis; however, there are instances where the underlying ocular inflammation may be refractory to NSAIDs and require escalation of therapy to systemic steroids or immunomodulatory agents (Figure 1). In instances where inflammation, pain, or visual outcomes have not improved in moderate scleritis immediately within a few weeks of NSAID therapy, it may be important to re-evaluate and consider escalation of therapy. Particularly, in cases of severe scleritis, necrotizing scleritis, and vasculitis-associated scleritis, NSAIDs may not be the ideal first-line agent, with important consideration needed for systemic steroids and IMT. There is wide variability in the use of IMT in the treatment of scleritis because of the variation in reported efficacy and treatment strategy in the literature on various classes of agents used; additionally, many of these studies also included patients with uveitis, which may affect the inability to conclude if there is any superior agent to use in treating scleritis. Physicians must therefore rely on clinical reasoning, given a lack of strong evidence-based medicine, at times, when making decisions on the appropriate agent to use in the treatment of scleritis. Antimetabolites may be a reasonable agent to consider when starting a patient on IMT for...
scleritis. This literature review supports methotrexate as a good starting point for the treatment of noninfectious scleritis requiring a steroid-sparing agent. This may need to be switched to other antimetabolites (mycophenolate or azathioprine) if methotrexate is ineffective or not tolerated by the patient. Biologic agents have also demonstrated efficacy in the treatment of scleritis. More studies are required to further refine the treatment algorithm for noninfectious scleritis, depending on clinical response and toleration of the medication.

**Literature search**
This review was compiled using articles identified by searching PubMed and Google. The following keywords were used for the search: ‘scleritis’, ‘inflammatory eye disease’, ‘scleritis and treatment’, ‘scleritis and NSAIDs’, ‘scleritis and steroids’, and ‘scleritis and immunomodulatory’. We included all relevant articles in English. Non-English articles were included if English abstracts were available.

**Author contributions**

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**Akash Gupta:** Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review and editing.

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**References**

1. Watson PG and Hayreh SS. Scleritis and episcleritis. *Br J Ophthalmol* 1976; 60: 163–191.

2. Smith JR, Mackensen F and Rosenbaum JT. Therapy insight: scleritis and its relationship to systemic autoimmune disease. *Nat Clin Pract Rheumatol* 2007; 3: 219–226.

3. Bin Ismail MA, Lim RHF, Fang HM, et al. Ocular Autoimmune Systemic Inflammatory Infectious Study (OASIS) – report 4: analysis and outcome of scleritis in an East Asian population. *J Ophthalmic Inflamm Infect* 2017; 7: 6.

4. Akpek EK, Thorne JE, Qazi FA, et al. Evaluation of patients with scleritis for systemic disease. *Ophthalmology* 2004; 111: 501–506.

5. Tuft SJ and Watson PG. Progression of scleral disease. *Ophthalmology* 1991; 98: 467–471.

6. Sainz de la Maza M, Jabbur NS and Foster CS. Severity of scleritis and episcleritis. *Ophthalmology* 1994; 101: 389–396.

7. Pavesio CE and Meier FM. Systemic disorders associated with episcleritis and scleritis. *Curr Opin Ophthalmol* 2001; 12: 471–478.

8. McGavin DD, Williamson J, Forrester JV, et al. Episcleritis and scleritis. A study of their clinical manifestations and association with rheumatoid arthritis. *Br J Ophthalmol* 1976; 60: 192–226.

9. Héron E and Bourcier T. Sclérites et épisclérites [Scleritis and episcleritis]. *J Fr Ophtalmol* 2017; 40: 681–695.

10. Cunningham ET Jr, McCluskey P, Pavesio C, et al. Scleritis. *Ocul Immunol Inflamm* 2016; 1: 2–5.

11. Tappeiner C, Walscheid K and Heiligenhaus A. [Diagnosis and treatment of episcleritis and scleritis]. *Ophthalmologe* 2016; 113: 797–810.

12. Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. *Surv Ophthalmol* 2016; 61: 1–17.

13. Stem MS, Todorich B and Faia LJ. Ocular pharmacology for scleritis: review of treatment and a practical perspective. *J Ocul Pharmacol Ther* 2017; 33: 240–246.

14. Rossi DC, Ribi C and Guex-Crosier Y. Treatment of chronic non-infectious uveitis and scleritis. *Swiss Med Wkly* 2019; 149: w20025.

15. 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: 1885–1891.
16. Bawazeer AM and Raffa LH. Adalimumab in the treatment of recurrent idiopathic bilateral nodular scleritis. Oman J Ophthalmol 2011; 4: 139–141.

17. Thueck PS and Stone DU. Certolizumab pegol therapy for rheumatoid arthritis-associated scleritis. Cornea 2012; 31: 90–91.

18. Jabs DA, Mudun A, Dunn JP, et al. Episcleritis and scleritis: clinical features and treatment results. Am J Ophthalmol 2000; 130: 469–476.

19. 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: 493–500.

20. Lavric A, Gonzalez-Lopez JJ, Majumder PD, et al. Posterior scleritis: analysis of epidemiology, clinical factors, and risk of recurrence in a cohort of 114 patients. Ocul Immunol Inflamm 2016; 24: 6–15.

21. Sainz de la Maza M, Molina N, Gonzalez-Gonzalez LA, et al. Scleritis associated with relapsing polychondritis. Br J Ophthalmol 2016; 100: 1290–1294.

22. Boonman ZFHM, De Keizer RJW and Watson PG. Smoking delays the response to treatment in episcleritis and scleritis. Eye 2005; 19: 949–955.

23. Yoshida A, Watanabe M, Okubo A, et al. 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: 417–424.

24. McCluskey P and Wakefield D. Intravenous pulse methylprednisolone in scleritis. Arch Ophthalmol 1987; 105: 793–797.

25. Sainz de la Maza MS, Molina N, Gonzalez-Gonzalez LA, et al. Scleritis therapy. Ophthalmology 2012; 119: 51–58.

26. Agrawal R, Lee CS, Gonzalez-Lopez JJ, et al. Flurbiprofen: a nonselective cyclooxygenase (COX) inhibitor for treatment of noninfectious, non-necrotizing anterior scleritis. Ocul Immunol Inflamm 2016; 24: 35–42.

27. Rosenbaum JT and Robertson JE Jr. Recognition of posterior scleritis and its treatment with indomethacin. Retina 1993; 13: 17–21.

28. Bauer AM, Fiehn C and Becker MD. Celecoxib, a selective inhibitor of cyclooxygenase 2 for therapy of diffuse anterior scleritis. Am J Ophthalmol 2005; 139: 1086–1089.

29. Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. Trans Am Ophthalmol Soc 2001; 99: 205–210; discussion 210.

30. Lin JC, Rapuano CJ, Laibson PR, et al. Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. Arch Ophthalmol 2000; 118: 1129–1132.

31. Sohn EH, Wang R, Read R, et al. Long-term, multicenter evaluation of subconjunctival injection of triamcinolone for non-necrotizing, noninfectious anterior scleritis. Ophthalmology 2011; 118: 1932–1937.

32. Albini TA, Zamir E, Read RW, et al. Evaluation of subconjunctival triamcinolone for nonnecrotizing anterior scleritis. Ophthalmology 2005; 112: 1814–1820.

33. Gangaputra SS, Newcomb CW, Joffe MM, et al. Comparison between methotrexate and mycophenolate mofetil monotherapy for the control of noninfectious ocular inflammatory diseases. Am J Ophthalmol 2019; 208: 68–75.

34. Sands DS, Chan SC and Gottlieb GC. Methotrexate for the treatment of noninfectious scleritis. Can J Ophthalmol 2018; 53: 349–353.

35. Kaplan-Messas A, Barkana Y, Avni I, et al. Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis. Ocul Immunol Inflamm 2003; 11: 131–139.

36. Daniel E, Thorne JE, Newcomb CW, et al. Mycophenolate mofetil for ocular inflammation. Am J Ophthalmol 2010; 149: 423–432.

37. Larkin G and Lightman S. Mycophenolate mofetil. A useful immunosuppressive in inflammatory eye disease. Ophthalmology 1999; 106: 370–374.

38. Kolomeyer AM, Ragam A, Shah K, et al. Mycophenolate mofetil in the treatment of chronic non-necrotic, non-necrotizing scleritis. Ocul Immunol Inflamm 2012; 20: 113–118.

39. Yağcındağ FN, Amer R and Forrester JV. Mycophenolate mofetil in the treatment of ocular inflammation in ANCA-associated vasculitis. J Ocul Pharmacol Ther 2008; 24: 249–254.

40. Hwang YS, Chen HC, Chen KJ, et al. Enteric-coated mycophenolate sodium as a corticosteroid-sparing agent for the treatment of autoimmune scleritis. Cornea 2011; 30: 260–264.

41. Thorne JE, Jabs DA, Qazi FA, et al. Mycophenolate mofetil therapy for inflammatory eye disease. Ophthalmology 2005; 112: 1472–1477.

42. Choudhary A, Harding SP, Bucknall RC, et al. Mycophenolate mofetil as an immunosuppressive agent in refractory inflammatory eye disease. J Ocul Pharmacol Ther 2006; 22: 168–175.
56. Gumus K, Mirza GE, Cavanagh HD, et al. Topical cyclosporine A as a steroid-sparing agent in steroid-dependent idiopathic ocular myositis with scleritis: a case report and review of the literature. Eye Contact Lns 2009; 35: 275–278.

57. Young AL, Wong SM, Leung AT, et al. Successful treatment of surgically induced necrotizing scleritis with tacrolimus. Clin Exp Ophthalmol 2005; 33: 98–99.

58. Miyazaki D, Tominaga T, Kakimaru-Hasegawa A, et al. Therapeutic effects of tacrolimus ointment for refractory ocular surface inflammatory diseases. Ophthalmology 2008; 115: 988–992.

59. Lee YJ, Kim SW and Seo KY. Application for tacrolimus ointment in treating refractory inflammatory ocular surface diseases. Am J Ophthalmol 2013; 155: 804–813.

60. Bhatt N, Dalal M, Tucker W, et al. Subconjunctival sirolimus in the treatment of autoimmune non-necrotizing anterior scleritis: results of a phase I/II clinical trial. Am J Ophthalmol 2015; 159: 601–606.

61. Pujari SS, Kempen JH, Newcomb CW, et al. Cyclophosphamide for ocular inflammatory diseases. Ophthalmology 2010; 117: 356–365.

62. Galor A and Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin North Am 2007; 33: 835–854.

63. De Fidelix TS, Vieira LA, De Freitas D, et al. Biologic therapy for refractory scleritis: a new treatment perspective. Int Ophthalmol 2015; 35: 903–912.

64. Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology 2014; 121: 785–796.

65. Huynh N, Cervantes-Castaneda RA, Bhat P, et al. Biologic response modifier therapy for psoriatic ocular inflammatory disease. Ocul Immunol Inflamm 2008; 16: 89–93.

66. Restrepo JP and Molina MP. Successful treatment of severe nodular scleritis with adalimumab. Clin Rheumatol 2010; 29: 559–561.

67. Pasut G. Pegylation of biological molecules and potential benefits: pharmacological properties of certolizumab pegol. Biodrugs 2014; 28(Suppl. 1): S15–S23.

68. Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory diseases.
eye disease and associated rheumatic disease. *Arthritis Rheum* 2001; 45: 252–257.

69. Ragam A, Kolomeyer AM, Fang C, et al. Treatment of chronic, noninfectious, nonnecrotizing scleritis with tumor necrosis factor alpha inhibitors. *Ocul Immunol Inflamm* 2014; 22: 469–477.

70. Durrani K, Kempen JH, Ying GS, et al. Adalimumab for ocular inflammation. *Invest Ophthalmol Vis Sci* 2012; 53: 5492.

71. Lawuyi LE and Gurbaxani A. Refractory necrotizing scleritis successfully treated with adalimumab. *J Ophthalmic Inflamm Infect* 2016; 6: 37.

72. Akhtar S, Babar S, Lightman S, et al. Adalimumab-induced remission of anterior scleritis: a very rare late manifestation of Takayasu arteritis. *Rheumatology* 2015; 54: 2288–2290.

73. 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* 2021; 105: 1256–1262.

74. 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: 1262–1268.

75. You C, Ma L, Lasave AF, et al. Rituximab induction and maintenance therapy in patients with scleritis and granulomatosis with polyangiitis (Wegener's). *Ocul Immunol Inflamm* 2018; 26: 1166–1173.

76. Recillas-Gispert C, Serna-Ojeda JC and Flores-Suárez LF. Rituximab in the treatment of refractory scleritis with granulomatosis with polyangiitis (Wegener's). *Graefes Arch Clin Exp Ophthalmol* 2015; 253: 2279–2284.

77. Cao JH, Oray M, Cocho L, et al. Rituximab in the treatment of refractory noninfectious scleritis. *Am J Ophthalmol* 2016; 164: 22–28.

78. Hardy S, Hashemi K, Cataneo M, et al. Necrotising scleritis and peripheral ulcerative keratitis associated with rheumatoid arthritis treated with rituximab. *Klin Monbl Augenheilkd* 2017; 234: 567–570.

79. Fidelix TS, Vieira LA and Trevisani VF. Management of necrotizing scleritis after pterygium surgery with rituximab. *Arq Bras Oftalmol* 2016; 79: 285–287.

80. Poelman HJ, Van Daele PLA and Rothova A. Successful tocilizumab treatment for scleritis. *Ocul Immunol Inflamm* 2020; 28: 915–920.

81. Gaujoux-Viala C, Giampietro C, Gaujoux T, et al. Scleritis: a paradoxical effect of etanercept? etanercept-associated inflammatory eye disease. *J Rheumatol* 2012; 39: 233–239.

82. Iwahashi C, Ono H, Haruta M, et al. New onset or exacerbation of uveitis with infliximab: paradoxical effects? *BMJ Open Ophthalmol* 2019; 4: e000250.

83. Gangaputra S, Newcomb CW, Liesegang TL, et al. Methotrexate for ocular inflammatory diseases. *Ophthalmology* 2009; 116: 2188–2198.e1.

84. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. *Ophthalmology* 2008; 115: 1826–1832.

85. Jeon HS, Hyon JY, Kim MK, et al. Efficacy and safety of immunosuppressive agents in the treatment of necrotising scleritis: a retrospective, multicentre study in Korea. *Br J Ophthalmol* 2016; 100: 1066–1070.