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Pharmacotherapy of Scleritis: Current Paradigms and Future Directions

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Abstract

Introduction—Scleritis is an inflammatory condition affecting the eye wall that may be associated with a number of systemic inflammatory diseases. Because scleritis can be refractory to standard treatment, knowledge of the body of available and emerging therapies is paramount and is reviewed here.

Areas Covered—This review focuses on both traditional and emerging therapies for non-infectious scleritis. We will cover the mechanisms of action and potential adverse effects of each of the treatment modalities. Additionally, a summary of the significant MEDLINE indexed literature under the subject heading “scleritis,” “treatment,” “immunomodulator” will be provided on each therapy, including commentary on appropriate use and relative contraindications. Lastly, novel treatments and potential drug candidates that are currently being evaluated in clinical trials with therapeutic potential will also be reviewed.

Expert Opinion—While oral non-steroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids are widely used, effective, first-line agents for inflammatory scleritis, refractory cases require anti-metabolites, T cell inhibitors, or biologic response modifiers. In particular, there is emerging evidence for the use of targeted biologic response modifiers, and potentially, for local drug delivery.

Keywords

Scleritis; therapy; anti-metabolite; alkylating agent; biologic response modifier; non-infectious

1. Introduction

1.1.

Scleritis is an inflammatory condition in which the outer shell of the eye, the sclera, becomes edematous and tender. The process is often acutely painful and the ocular morbidity can be significant due to complications including decreased vision, uveitis, glaucoma, and rarely, globe perforation. While there are few population-based studies investigating its incidence or prevalence, one study roughly estimated a prevalence of 6 cases per 10,000 people.¹ Scleritis is associated with underlying systemic disease in approximately 36–57% of patients depending on the clinic setting and referral patterns.^{2, 3} The disease can be classified in numerous ways: anterior or posterior, nodular or diffuse, necrotizing or non-necrotizing, and infectious or non-infectious. It is important to note that

while lab tests may assist in the diagnosis of an underlying systemic disease, the diagnosis of scleritis remains a clinical one.

Anterior, non-necrotizing, non-infectious scleritis is the most common form, and it is further characterized as diffuse or nodular.⁴ In scleritis there is dilation of the superficial and deep episcleral vasculature resulting in a violaceous or bluish-red hue in the section of the sclera involved. The nodular form is present if there is a visible elevation with engorged scleral vessels. Scleritis can be unilateral or bilateral, and is usually exquisitely painful. Instillation of phenylephrine will not blanch the scleral vessels and can be a useful test to differentiate between episcleritis and scleritis. Unless there is concurrent involvement of the cornea or uveal tract, the vision is minimally affected in acute disease. Systemic disease associations of scleritis include rheumatoid arthritis (RA), relapsing polychondritis, granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), sarcoidosis, Sweet syndrome, the seronegative spondyloarthropathies, and multiple forms of systemic vasculitis including but not limited to Behçet's disease and Takayasu's arteritis.^{5, 6} In about 50% of cases, no underlying systemic disorder is identified. Necrotizing anterior scleritis without inflammation, also referred to as scleromalacia perforans, is a unique process that is generally painless and, despite the name, rarely leads to globe perforation. Often, the underlying uveal tissue is visible through the thinned sclera giving it a blue-gray to brown appearance. This condition is associated with rheumatoid arthritis and is typically bilateral.⁷ Surgically induced necrotizing scleritis is a rare condition that is presumably autoimmune and follows multiple surgical traumas to the eye.⁸

Posterior scleritis is inflammation of the sclera that is behind the orbital septum and is not visible to the casual observer. This process is usually unilateral and can be associated with significant pain, especially on eye movement but may also be painless. An underlying systemic association is found in 29% of patients.⁹ Eye redness in posterior scleritis is typically absent unless there is an anterior component. Visual acuity usually remains unchanged unless there is a refractive shift from altering the curvature of the posterior globe, or when associated with a serous retinal detachment or optic nerve head edema. B-scan ultrasonography can demonstrate a characteristic "T sign," corresponding to the presence of fluid in the sub-Tenon's space surrounding the optic nerve.

An infectious cause is responsible for about 5–10% of cases of anterior scleritis. The infecting organisms include bacteria, viruses, parasites, or fungi. Most infectious scleritis is classically associated with antecedent trauma, surgical manipulation, such as pterygium excision^{10, 11}, cataract extraction¹², strabismus surgery¹³, or vitrectomy.¹⁴ Scleral buckling is also a risk factor for the development of infectious scleritis.^{14, 15} Trauma and prior surgery accounted for 89% of cases of infectious scleritis in a recent large series.¹² While the presentation can be similar to non-infectious scleritis with a red, tender eye, non-response to steroids especially in an eye that has had prior trauma should lead to clinical suspicion of an infectious source. Treatment is with aggressive local and systemic antibiotics as well as surgical debridement. The outcome of infectious scleritis is generally worse than with non-infectious scleritis, with only 33–50% of eyes retaining vision better than 20/200 after treatment, and up to 25% of eyes requiring enucleation.^{12, 16} The remainder of this paper will focus on therapeutic options for non-infectious scleritis rather than infectious scleritis.

2. Current Opinions

2.1. First line therapies for non-infectious scleritis

2.1.1. Topical and local therapies

2.1.1.1. Topical steroids: Topical prednisolone acetate 1% is often used for mild cases of anterior scleritis associated with intraocular inflammation. While its ease of use and relatively minimal side effect profile when compared to systemic therapy are advantageous, scleritis does not usually respond to topical corticosteroids alone. One study reported a 47% success rate, defined as resolution of scleritis without the need for systemic steroids or NSAIDs at 2 months.¹⁷ However, most clinicians treating scleritis at tertiary care referral centers conclude that topical therapy alone has a high failure rate, and that the vast majority of patients with scleritis require systemic therapy.^{1, 4} In our patient population, this lack of efficacy generally restricts this agent to an adjunctive role supplementing more definitive therapy, which will be described below.

2.1.1.2. Sub-Conjunctival/Sub-Tenon's Triamcinolone: Local injection of triamcinolone has been in the armamentarium of ophthalmologists to treat everything from cystoid macular edema to recalcitrant intermediate uveitis for over 30 years. However, previous case series suggested that administration of periocular steroid injections in scleritis patients increased the risk of progressive scleral necrosis and perforation.¹⁸ As a result, this procedure was avoided for years until more recent case reports demonstrated efficacy and safety in non-necrotizing, non-infectious scleritis.^{19, 20} A recent multicenter retrospective case series of 68 eyes with either diffuse or nodular scleritis showed that 89.7% of eyes had complete resolution after a single injection. The effect was durable in 50% of patients out to 48 months. 34% of patients required a second injection to retain disease remission.²¹ Of the patients on systemic therapy for their scleritis, 96% were taking some form of immunosuppressive therapy prior to injection whereas 43% were taking these medications at last follow up. There were no reported cases of perforation or scleral melt and the most common attributed side-effect of the triamcinolone was elevated intraocular pressure in 20% of eyes.²¹ Local injection of triamcinolone should only be considered if the inflammation is nonnecrotizing. Caution should be utilized in cases associated with an elevated intra-ocular pressure or in patients with known steroid-responsive ocular hypertension. Our practice has some success treating posterior scleritis with posterior subtenon's triamcinolone although there appears to be a lack of published literature on this treatment for this indication.

2.1.2. Oral NSAIDs—Oral non-steroidal anti-inflammatory drugs act by inhibiting the enzyme, cyclooxygenase, thus suppressing the synthesis of many metabolites of arachidonic acid. They are considered first-line therapy for scleritis for their ease of use, cost, and relatively mild side effect profile. Both anterior^{18, 22} and posterior scleritis^{9, 23} may respond well to NSAID therapy. The choice of which medication to use is often based on availability and side effect profile, though the most commonly used include indomethacin, naproxen, and ibuprofen (Table 1). While short term use of an NSAID is often well tolerated, NSAIDs can cause adverse effects which include peptic ulcer disease, hypertension, increased heart disease, bleeding, fluid retention, renal disease, and mood change. The COX-2 inhibitor celecoxib has also shown good efficacy.²⁴ Because of its selectivity to COX-2, it carries the advantage of having a lower risk of gastrointestinal (GI) bleeding than other NSAIDs. Semi-selective NSAIDs such as etodolac are thought to cause less GI blood loss than non-selective NSAIDs,²⁵ and in our experience, have been effective in the treatment of scleritis as well.

2.1.3. Corticosteroids—Oral prednisone is widely considered to be the first line therapy for the treatment of non-necrotizing scleritis in the setting of poor control on oral NSAIDs,

or as a first line agent for necrotizing scleritis.^{4, 26, 27} The doses are titrated to clinical improvement, but usually begin at 40 to 60 mg daily, and then the dosage is reduced with a slow taper.¹ If after 1 month there is a minimal or partial response, another agent may be required.⁴ For patients intolerant of oral steroids, intravenous methylprednisolone has been shown to be efficacious in scleritis.^{28, 29} If the patient remains symptomatic on a dose of 10 mg/day or more, alternative therapy must be added to reduce the risk of long term corticosteroid-induced morbidities. For any patient on steroid therapy, careful monitoring of blood glucose, lipids, bone density, mental status, weight changes, and GI symptoms should be performed. Calcium (1200 mg) and Vitamin D 800–1000 IU daily are recommended with long-term steroid use to prevent osteopenia. Care should be taken to avoid co-administering NSAIDs and corticosteroids as this greatly increases the incidence of GI ulceration (relative risk of 4.4 with steroids in combination with NSAIDs compared with 1.1 for steroids alone).³⁰

2.1.4. Antimetabolites

2.1.4.1.: Methotrexate was originally introduced as an anti-neoplastic drug in 1948 but its primary use is in systemic rheumatic diseases, where it has shown efficacy in rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriatic arthritis, and SLE.³¹ It is a dihydrofolate reductase inhibitor that acts on the thymidylate synthesis pathway to decrease the production of rapidly dividing cells. In addition to decreasing cellular proliferation of immune cells, it enhances T-lymphocyte apoptosis, and alters cytokine production.³² Methotrexate has a long history of use in uveitis treatment as a steroid-sparing agent in both juvenile^{33, 34} and adult disease³⁵ in a wide range of inciting conditions. In a retrospective review of 56 patients within the Systemic Immunosuppressive Therapy for Eye Disease (SITE) cohort treated with methotrexate as monotherapy for scleritis, good control of inflammation, as defined by quiescence of symptoms on methotrexate and 10 mg of prednisone, was achieved in 37.3% of patients at six months and 58.3% at 12 months (Table 2). 17% were able to achieve remission on methotrexate alone at one year. 16% of patients had to discontinue the medicine due to side effects, and 2.3% for elevated liver function tests.³⁵ A smaller study of 18 patients showed controlled inflammation in 11 (61%), of whom ten (91%) were taking prednisone 10 mg a day.³⁶ Fatigue was noted in 6/18 (33%) patients and there were no cases of elevated lab values or cirrhotic liver disease. Fatigue, elevated liver enzymes, and nausea are the most common side effects, but rare cases of cirrhosis, interstitial pneumonitis, and cytopenia have been reported.^{22, 35} Patients who regularly consume alcohol should use a different agent if they are unwilling to lower their alcohol intake to two drinks per month or less. Folic acid 1 mg PO daily should be taken with methotrexate to reduce the risk of bone marrow suppression. A complete blood count (CBC) and liver function tests (LFTs) should be evaluated every two months while on any anti-metabolite. A baseline hepatitis panel is also recommended prior to initiating methotrexate.

2.1.4.2.: Azathioprine (AZA), first synthesized in 1957, has a long history of use in transplant rejection therapy. As a purine nucleoside analog, it inhibits proliferation of circulating T and B cells through interference with DNA and RNA transcription.²² In addition to treating transplant rejection, it is effective in rheumatoid arthritis, psoriatic arthritis, reactive arthritis, Behçet's disease, and SLE.³⁷ In the SITE cohort, of the 16 patients who were treated with azathioprine as a steroid-sparing agent for scleritis, 22.2% were quiescent at six months and 35.2% at 12 months on less than 10 mg of prednisone. 11.1% of patients achieved quiescence off prednisone at 12 months (Table 2). Of the total cohort, 24% discontinued AZA because of side effects, the most common being GI disturbance, bone marrow suppression, and elevated liver enzymes.³⁸ Some patients must discontinue AZA due to a flu-like response that usually starts about one month after starting

this medication. A review of the antimetabolites in ocular inflammatory disease concluded that AZA had a higher rate of side effects, most commonly those noted above, than either methotrexate or mycophenolate.³⁹ Patients who have deficient thiopurine methyltransferase (TPMT) activity may be at increased risk of myelosuppression and poor treatment response to AZA due to alterations in the metabolism of the drug resulting in buildup of the drug's toxic metabolite, 6-thioguanine.⁴⁰ For this reason, some clinicians advocate for testing of red blood cell TPMT activity prior to initiating this drug or in patients who develop leukopenia on treatment.⁴¹

2.1.4.3.: Mycophenolate mofetil (MMF) is a selective inhibitor of inosine monophosphate dehydrogenase that interrupts guanosine synthesis, leading to decreased T and B lymphocyte proliferation, reduced antibody production, and decreased leukocyte transmigration.²² MMF has been used as an anti-rejection medication for cardiac and renal allografts.⁴² The SITE cohort reported that of the 51 eyes from 33 scleritis patients that were treated with MMF, 25.5% had successful control of inflammation at 6 months and 49.5% at 12 months while on prednisone 10 mg (Table 2). Complete therapeutic success, i.e. control of inflammation off all steroids, occurred in 7.1%.⁴³ Other studies demonstrated a success rate of 42–55% on 10 mg or less of prednisone.^{2, 44} Of the total SITE cohort, 12% discontinued the medication secondary to side effects, the most common being GI upset, bone marrow suppression, and elevated liver enzymes.⁴³ Side effect rates are similar to that of methotrexate but less than azathioprine.³⁹ GI side effects are decreased with dose reduction, without substantial loss of efficacy.^{22, 45} The authors usually select methotrexate as the first line anti-metabolite because of the ease of weekly usage and its lower cost relative to MMF, though the lower rate of liver toxicity makes MMF first-line in patients who are unwilling to discontinue use of alcohol.

2.1.5. Alkylating agents

2.1.5.1.: Cyclophosphamide is an alkylating agent that causes cross-linking of RNA and DNA leading to cell death. This agent is cytotoxic to active and resting T and B lymphocytes and therefore suppresses both the humoral and cellular immune response.^{22, 46} This medication has been successfully used as an anti-neoplastic agent as well as in SLE nephritis, mucous membrane pemphigoid⁴⁷, and systemic vasculitis, particularly that associated with granulomatosis with polyangiitis.^{48, 49} Within the eye, its primary uses are in the treatment of systemic vasculitis-associated ocular disease and ocular cicatricial pemphigoid.⁵⁰ In the SITE cohort, 76 eyes of 48 patients with scleritis were treated with cyclophosphamide, 47.9% of whom were treated with another immunosuppressant first. 30.2% of patients achieved treatment success at 6 months on less than 10 mg of prednisone and 60.5% were controlled at 12 months. 15.9% were controlled at 12 months on cyclophosphamide alone (Table 2). It is important to highlight that in the presence of systemic inflammatory disease (e.g. due to GPA, polyarteritis nodosa, or relapsing polychondritis), the underlying disease should be treated to control both the scleral inflammation, which can be sight threatening, as well as the systemic disease, which might carry a high rate of mortality without treatment. While in the past, cyclophosphamide was used to treat some of these potentially life-threatening systemic diseases such as GPA, biologic agents, such as rituximab for GPA and infliximab for refractory polychondritis, have more recently been used successfully, obviating the need to use an alkylating agent. The latter two agents will be described in more detail later. Of the total SITE cohort, 33.5% discontinued cyclophosphamide from side effects, the most common including leukopenia (18.1%), cystitis (7.7%), and anemia (3.3%). 2.3% of patients developed an opportunistic infection and one patient in the cohort died from pneumocystis pneumonia.⁵⁰ There is an increased rate of malignancy, particularly bladder cancer, in patients on cyclophosphamide.⁵¹ There is some controversy regarding whether relatively low dose,

short term use of chemotherapeutics in ocular disease may reduce the overall risk of malignancy.⁵² A review of the SITE cohort found a trend that was not statistically significant for an increase in cancer-related mortality in the 486 patients treated with an alkylating agent, although all-cause mortality was not affected.⁵³ An expert panel recommended that cancer screening for patients on alkylating therapies is a prudent step, even if the dosage and treatment times for ophthalmic disease is less than for systemic disease.²² With this in mind, alkylating agents should be dosed in a manner that can reduce the patient's overall exposure to the drug and still achieve disease remission.^{1, 54}

2.1.5.2.: Chlorambucil is an alkylating agent used in the treatment of leukemia, lymphoma, and ovarian carcinoma. Its overall use outside of oncology is less frequent than for cyclophosphamide, though there are multiple reports of its successful use in Behçet's disease.^{55, 56} Small case series demonstrate its efficacy in ophthalmic inflammatory disease including sympathetic ophthalmia, Behçet's vasculitis, and serpiginous choroiditis.^{57, 58} Goldstein et al reported 4 out of 5 scleritis patients treated with chlorambucil had sustained remission off of steroids, suggesting that this medication may be effective for scleritis as well.⁵⁹ For induction of drug-free remission, doses are titrated to suppress WBC counts within a narrow range (between 2800–3000/mm³). While this group and others have reported success in treating scleritis with chlorambucil, this drug has a particularly severe side effect profile, causing secondary malignancy, secondary amenorrhea in women, testicular dysfunction in men, alopecia, herpes zoster reactivation, and rarely, transfusion-requiring thrombocytopenia.⁵⁹

2.1.6. T cell Inhibitors

2.1.6.1.: Tacrolimus is a naturally occurring macrolide antibiotic produced by *Streptomyces tsukubaensis* that acts as a T cell inhibitor by inhibiting calcineurin and subsequently nuclear factor of activated T-cells (NFAT), a transcription factor that promotes T cell replication.⁶⁰ The most common use is in solid organ transplant as an anti-rejection medication, often utilized after failure with cyclosporine.⁶¹ Its use in scleritis is not well-documented, but one case report demonstrated success for surgically induced necrotizing scleritis in a patient who previously failed cyclophosphamide and azathioprine.⁶² The major dose-limiting effect of tacrolimus is similar to cyclosporine, since it can cause renal insufficiency (28% in one series) and hypertension (48–54%).^{4, 63}

2.1.6.2.: Cyclosporine is a natural product of fungi that inhibits T cell replication by preventing the translocation of NFAT by binding to calcineurin. The process both prevents cell replication and causes the upregulation of interleukin-2 and interferon beta.^{64, 65} Outside of ophthalmology, its main uses are in transplant medicine, rheumatoid arthritis, and plaque psoriasis. Within ophthalmology, a prospective trial demonstrated that cyclosporine was significantly more effective for the treatment of the ocular manifestations of Behçet's disease when compared to colchicine.⁶⁶ However, the dosage of cyclosporine used in this study is frequently nephrotoxic. We currently recommend a dosage of 2.5 to 5 mg/kg/day in a divided dosage with careful monitoring of blood pressure and renal function as described below. For scleritis, the largest study is again the SITE cohort, which evaluated 23 eyes of 15 patients and found steroid sparing success (on prednisone 10 mg) in 52.8% at 6 months and 52.8% at 12 months. 25% of patients were able to entirely stop prednisone (on cyclosporine alone) at 12 months (Table 2).⁶⁷ Other case reports demonstrated the efficacy of cyclosporine in scleritis associated with Cogan's syndrome⁶⁸, as topical therapy for necrotizing scleritis⁶⁹, and in rheumatoid arthritis-associated scleritis⁷⁰. The most common side effects in the SITE cohort necessitating medication discontinuation were renal insufficiency (4.3%) and hypertension (3.2%). There was also a higher rate of discontinuation among the > 55 year-old cohort and in patients taking doses higher than 250

mg per day due to medication-induced side effects. For this reason, care is urged in using cyclosporine in the older age group and bimonthly monitoring of blood pressure and renal function is recommended in all patients^{22, 67}. Gingival hyperplasia, muscle cramps, hirsutism, and neurologic symptoms including headaches, tremors, and paresthesias are also common while taking cyclosporine.

2.1.7. Antibiotics

2.1.7.1.: Dapsone (4,4-diaminodiphenyl sulfone), is an antibiotic that functions as an anti-inflammatory drug in the treatment of a variety of conditions including leprosy and bullous pemphigoid⁷¹. It has shown efficacy in treating mild cases of ocular cicatricial pemphigoid.^{72, 73} There are few reports of dapsone used in the treatment of relapsing polychondritis-associated scleritis.⁷⁴ In one small series, dapsone controlled inflammation in 2 of 4 patients with diffuse anterior scleritis. However, in another case series by Hoang-Xaun et al it failed to control inflammation in 6 of 8 patients with necrotizing scleritis.⁷⁵ Dapsone has also been used in the treatment of Sweet syndrome-(acute febrile neutrophilic dermatosis) associated nodular scleritis as adjunctive therapy.^{76, 77} The main dose-related toxicity is methemoglobinemia in nearly all patients, and hemolytic anemia in patients, especially those with G6PDH deficiency.⁷⁸

2.2. Second line therapies

2.2.1. Anti- TNF Agents

2.2.1.1.: Etanercept is a dimeric fusion protein consisting of a human IgG1 Fc fragment linked with the soluble tumor necrosis factor (TNF) receptor 2 that binds to both alpha and beta isoforms of TNF, rendering them unable to bind to their cell surface receptors. This interrupts the inflammatory cascade resulting in a decrease in cytokine expression and leukocyte adhesion factors.⁷⁹ The drug is approved in the treatment of RA, JIA, ankylosing spondylitis (AS), plaque psoriasis, and psoriatic arthritis. Etanercept has been evaluated for the treatment of scleritis with mixed efficacy (Table 3). A report of 6 patients treated with etanercept for RA-associated scleritis demonstrated clinical improvement in 2 (33%).⁸⁰ A separate retrospective report of ten patients with scleritis treated with etanercept showed good efficacy with minimal side effects.⁸¹ However, etanercept has also been reported to cause uveitis, either as a result of a flare of pre-existing disease^{80, 82}, or leading to *de novo* uveitis while on therapy for RA⁸³. While there are no reports of etanercept-induced scleritis, most would tend to avoid etanercept as therapy for ocular inflammation and will instead use a monoclonal antibody such as adalimumab or infliximab. Both seem to have greater potency in ocular inflammation with a lower likelihood of worsening disease.^{39, 84} The major side effects of TNF inhibitors tend to be a class effect, and include an increase in serious infections, reactivation of latent tuberculosis, progressive multifocal leukoencephalopathy, heart failure, demyelinating disease, and anemia. The SITE cohort study found that TNF inhibitors as a class, but not individually, have a statistically significant increase in cancer mortality and all cause mortality.⁵³ However, the sample size was too small and the follow-up duration too short to recommend modification of treatment with this class of drugs.

2.2.1.2.: Infliximab is a chimeric monoclonal antibody that binds to TNF alpha and blocks its activity. It inhibits multiple cell types and induces cell death via the complement pathway or by recognition by cytotoxic cells. It is FDA approved for use in RA, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriasis. Within the eye, infliximab has shown efficacy in Behçet's Disease-related uveitis^{85, 86}, a host of other uveitic conditions⁸⁷, as well as juvenile idiopathic arthritis⁸⁸, sympathetic ophthalmia⁸⁹, and Vogt- Koyanagi-Harada syndrome.⁹⁰ A number of case reports support its use in scleritis.⁹¹⁻⁹⁴ A prospective

series from the National Eye Institute showed resolution of scleritis in five patients treated with this drug, but the authors noted that one patient developed treatment-resistant intraocular inflammation.⁹⁵ A larger, prospective series of refractory uveitis patients treated with infliximab demonstrated a good response in 24 of 31 (78%) patients, but also showed a relatively high rate of adverse events including two with thromboembolism, three with drug-induced lupus, and two patients who developed solid malignancies.⁹⁶

2.2.1.3.: Adalimumab is a fully human IgG1 antibody directed against TNF-alpha which blocks its activity at the TNF receptor on the cell surface of fibroblasts, neutrophils, and vascular endothelial cells, resulting in complement-induced cytotoxicity.⁹⁷ It is FDA approved for use in RA, inflammatory bowel disease, AS, psoriatic arthritis, and JIA. In the treatment of inflammatory eye disease, adalimumab has shown efficacy in uveitis secondary to JIA⁹⁸, AS⁹⁹, idiopathic orbital inflammation¹⁰⁰ and Behçet's disease.¹⁰¹ There are a few case reports of its use in refractory scleritis with good effect.^{102, 103} Given the class effect, it is likely that adalimumab would be effective in larger series as well, though further data are needed to verify a treatment effect. A rare hepatosplenic lymphoma has been reported mostly in children receiving both adalimumab or other TNF inhibitor and azathioprine¹⁰⁴.

2.2.1.4.: Certolizumab, a pegylated humanized monoclonal antibody, and golimumab, a humanized monoclonal antibody, are newer anti-TNF agents marketed for use in RA, AS, IBD, and psoriatic arthritis. While the ophthalmic literature supporting their use is currently small, there are scattered case reports of efficacy in refractory uveitis and scleritis.^{105–107}

2.2.2. Other Biologic therapies

2.2.2.1. Anti-CD20: Rituximab is a chimeric murine/human monoclonal antibody against the CD20 antigen on human B cells. It results in the depletion of B-cells and B-cell precursors, though long-lived plasma cells and stem cells are not affected. Rituximab lowers the levels of circulating IgG and IgM antibody as well as their B-cell source for 6 to 12 months or more.^{84, 108} It is most commonly used in the treatment of non-Hodgkins lymphoma, multiple myeloma, and chronic lymphocytic leukemia. Rituximab has been shown to be non-inferior to cyclophosphamide in the treatment of GPA¹⁰⁹ and it is now FDA-approved for this indication. Within the eye, there are cases to support its use in ocular cicatricial pemphigoid¹¹⁰, GPA¹¹¹, Sjogren's disease¹¹², and Behçet's disease.¹¹³ This drug can be used to treat intraocular lymphoma as well as orbital disease, particularly those mediated by B-cells, such as Graves' Disease. There are case reports of its efficacy in treating scleritis, in particular as a manifestation of systemic disease such as RA^{114, 115}, Sjogren's¹¹⁶, and GPA^{117, 118}. The largest published series in uveitis to date looked at 8 children with refractory uveitis and found that rituximab was effective in allowing prednisone reduction in all subjects.¹¹⁹ A report presented by our group at the ARVO meeting in 2011 suggested that 9 of 12 patients with refractory scleritis showed evidence of reduced scleritis disease activity within six months of receiving rituximab infusions.¹²⁰ The major side effects of rituximab include an increased potential for serious infections, Stevens-Johnson Syndrome, infusion reaction, pulmonary edema, and progressive multifocal leukoencephalopathy.

2.2.2.2. Anti –CD25: Daclizumab is a humanized monoclonal antibody to the CD25 subunit on the IL-2 receptor on T cells that functions to inhibit actively proliferating T cells but not their resting counterparts.¹²¹ It showed some efficacy in inflammatory eye disease, but is no longer commercially available.¹²²

2.2.2.3.: Campath was one of the first biologic therapies tested in the treatment of uveitis. It is a monoclonal antibody against CD52, a cell surface marker found on all B and T cells. It may be effective in treating Behçet's disease,¹²³ JIA-associated uveitis¹²⁴, and peripheral

ulcerative keratitis associated with GPA.¹²⁵ In a series of ten patients with recalcitrant ocular inflammation from a variety of etiologies, a sustained response was achieved in two scleritis patients.¹²⁶

2.2.3. Biologic Agents Under Investigation—Each of the following agents has shown efficacy in systemic inflammatory disease and is under active investigation for its use in ocular disease. It should be noted that none has shown to be useful in the treatment of scleritis to date, and they are mentioned only as potential therapies that need to be proven useful. The rationale for their potential efficacy lies in the importance of the targeted cytokine in the pathogenesis of systemic diseases associated with scleritis. For instance, targeting IL-6 and IL-1 with Tocilizumab and Anakinra, respectively, appears to be important in rheumatoid arthritis.^{127, 128}

2.2.3.1. Anti IL-6: Tocilizumab is a monoclonal antibody against the IL-6 receptor that has been shown to be effective in RA and JIA, particularly when recalcitrant to anti-TNF therapies.¹²⁸ The data for its use in ocular inflammation are scarce. One group reported that 2 of 3 eyes with JIA-associated uveitis improved¹²⁹ while another showed improvement in 2 eyes treated for refractory uveitis.¹³⁰

2.2.3.2.: Abatacept is a soluble fusion protein that consists of human cytotoxic T lymphocyte antigen 4 linked to IgG1 that binds to CD80/CD86 and blocks the costimulatory signal at CD28 and prevents T cell activation. It has been shown to be efficacious in the treatment of RA.¹³¹ Its use in ophthalmology has thus far been limited to JIA in case reports. In each of the case reports, it has demonstrated efficacy with minimal side effects.^{132, 133}

2.2.3.3.: Anakinra is an IL-1 receptor antagonist that blocks the binding of IL-1 alpha or IL-1 beta to its receptor. It is effective treatment for moderate to severe RA and has many beneficial effects in articular disease including inhibition of bone resorption and decreased cartilage degradation.¹³⁴ It has been reported to be efficacious in Chronic Infantile Neurologic, Cutaneous and Articular (CINCA) syndrome¹³⁵ and is beneficial in murine models of disease¹³⁶ but more work is needed to assess its utility in scleritis.

2.2.3.4.: Many other biologic therapies have the potential to treat ocular inflammation given their efficacy in small trials for systemic disease. However, no published data exist to demonstrate efficacy in the eye or scleritis in particular. Natalizumab (anti-alpha4 integrin), ustekinumab (anti-IL-23/IL-12), and tofacitinib (a small molecule JAK kinase inhibitor approved to treat refractory rheumatoid arthritis) are effective in the treatment of various systemic inflammatory diseases and may be useful in the treatment of scleritis, though this has not been tested.

2.2.4. Newer local treatment—A phase I clinical trial of the mammalian target of rapamycin (mTOR) inhibitor, sirolimus, given as a subconjunctival injection for the treatment of immune-mediated, non-necrotizing anterior scleritis currently enrolling patients. (www.clinicaltrials.gov) In addition to new pharmacotherapeutics, advances in drug delivery may prove to enhance the delivery of first-line agents to the sclera, and may have the additional benefit of reduced systemic side effects. For instance, an iontophoretic device (Eyegate Pharmaceuticals) that enhances the movement of dexamethasone across the cornea and the conjunctiva has been developed for the treatment of uveitis and scleritis and is currently in Phase III and Phase I clinical trials, respectively. By creating a weak electrostatic field, the device propels corticosteroid molecules across tissue planes to achieve a high concentration within the eye.¹³⁷

3. Conclusions

3.1.

There is a wide range of choices for the treatment of scleritis, from non-specific, but highly effective corticosteroids to monoclonal antibodies targeting an inciting molecule. Corticosteroids have the advantage of rapid control of inflammation, but carry many systemic risks with long-term therapy. Immunomodulatory therapy can sustain inflammatory control without the same side effects that can be caused by long-term steroid use. Biologic agents represent alternative regimens that spare patients from long term steroid therapy while targeting a more specific pathway. They may also prove to be useful in refractory cases of scleritis. Finally, improvements in drug delivery may refine the treatment of scleritis that is not associated with systemic disease by avoiding medications that are associated with systemic toxicity.

4. Expert Opinion

The mainstay of therapy for non-infectious scleritis includes oral NSAIDs and oral prednisone, while topical steroids remain useful when there is co-existing intraocular inflammation or mild disease. Subconjunctival injection of triamcinolone may also be an effective treatment for non-infectious, non-necrotizing anterior scleritis, although early concerns for scleral melt have limited its widespread use, and it would not be appropriate as sole therapy in the presence of associated systemic disease requiring systemic therapy.

It is our practice to institute steroid-sparing therapy if the patient cannot be successfully tapered below 10 mg of prednisone without symptoms or clinical signs of active scleritis. We generally start with an anti-metabolite (typically starting with methotrexate) and tailor the choice to individual patient characteristics such as alcohol intake and systemic co-morbidities. Should one anti-metabolite fail or cause untoward side effects, then we will institute a prednisone pulse and change to a different anti-metabolite. If mild disease activity persists despite the above treatment, a non-steroid adjunctive treatment can be added such as a calcineurin inhibitor.

Biologic response modifiers have great potential in the treatment of scleritis. Currently, the data are lacking to demonstrate efficacy as a first line agent except in the presence of known auto-inflammatory diseases such as RA. In the setting of multiple drug failure, biologics provide a reasonable option for the treatment of recalcitrant scleritis. Based on our own experience with rituximab, we consider this medication for patients with scleritis who have proven refractory to oral corticosteroids and at least one other immunosuppressive medication.

The main challenges in the treatment of non-infectious scleritis lie in the rarity of the disease and the diversity of etiologies that can cause inflammation of the sclera. Because of the former, there is a paucity of multi-centered studies demonstrating efficacy of certain drugs for patients with scleritis, other than the SITE cohort studies. Furthermore, because scleritis is not caused by a single etiology, but rather a number of different etiologies, extrapolating a treatment effect from small case series to other patients is difficult. Multi-centered studies on treatment effects in different types of scleritis would begin to allow clinicians to target treatment more effectively. Another challenge in the treatment of scleritis is balancing systemic toxicity with effectiveness of treatment. In this regard, local therapy through drug delivery techniques such as iontophoresis, and sustained drug delivery devices that can be injected or implanted in the eye, may be the future of therapeutic success for this condition.

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Article Highlights

- Rapid diagnosis of scleritis and institution of appropriate therapy are important to prevent systemic and ocular morbidity.
- Scleritis is often associated with underlying systemic inflammatory disease.
- First line therapy for non-infectious scleritis includes non-steroidal anti-inflammatory drugs and local or systemic corticosteroids.
- Immunomodulatory therapy with anti-metabolites and T cell inhibitors is sometimes required to reduce the steroid burden and maintain disease remission after initial control with corticosteroids.
- Biologic response modifiers are potential therapies for scleritis that target specific molecules in the inflammatory cascade.

Table 1

First-line therapeutics for non-infectious scleritis

Drug	Dosage/Route	Side Effects	Estimated Efficacy
NSAIDs (representative examples)		Fluid retention, dyspepsia, GI bleeding, perforation/ulcer, nephrotoxicity, cardiac disease	33.3% response rate in diffuse anterior scleritis patients, 57.1% response rate in nodular scleritis patients ⁴
Ibuprofen (Non-selective)	600–800 mg PO TID to QID	As above	
Indomethacin (Non-selective)	25–50 mg PO TID to QID 75 mg SR PO BID	As above	
Naprosyn (Non-selective)	250–500 mg PO BID	As above	
Celecoxib (Selective)	100–200 mg PO BID	Less GI bleeding than non-selective NSAIDs	Remission in 22 of 24 eyes ²⁴
Triamcinolone (40 mg/mL)	2–8 mg by subconjunctival injection in 1 to 4 quadrants	Globe perforation, elevated IOP, cataract	67.6% remained recurrence-free at 2 years after a single injection ²¹
Prednisone	40–60 mg PO daily with slow taper over 4–6 weeks	Cushing's syndrome, insomnia, glucose intolerance, muscle weakness, hypertension, mood swings, sodium and fluid retention	Response in nearly every case; Inability to reduce dose in 26% ⁴

NSAIDs: non-steroidal anti-inflammatory drugs; GI: gastrointestinal; PO: by mouth; IOP: intraocular pressure

Table 2

Steroid-sparing immunosuppressive drugs used in the treatment of scleritis

Drug	Dosages/Route	# scleritis patients ¹	*Treatment success within 6 months of initiating therapy %	*Treatment success within 6 months of initiating therapy %	*Treatment success within 12 months of initiating therapy %	*Treatment success within 12 months of initiating therapy %	Side effects
Methotrexate	12.5–25 mg PO/SC weekly	56	37.3	4.3	58.3	17.5	Nausea, fatigue, hepatotoxicity, interstitial pneumonitis, cirrhosis, cytopenia
Azathioprine	1–2.5 mg/kg/day PO	16	22.2	0.0	35.2	11.1	Nausea, vomiting, hepatotoxicity, bone marrow suppression
Mycophenolate	2–3g/day PO in divided doses	33	25.5	7.1	49.4	7.1	Dyspepsia, hepatotoxicity, bone marrow suppression
Cyclophosphamide	1–2 mg/kg PO daily	48	30.2	0.0	60.5	15.9	Leukopenia, cystitis, anemia, opportunistic infections, malignancy, sterility, hair loss
Cyclosporine A	2.5–5.0 mg/kg/day PO in a divided dose	15	52.8	16.7	52.8	25.0	Nephrotoxicity, hypertension, gingival hyperplasia, hirsutism, muscle cramps, neurological symptoms (paresthesia, tremor, headaches)

PO: by mouth; IV: intravenous; SC: subcutaneous; CBC: complete blood count; CMP: complete metabolic panel

Table 3

Biologic response modifiers used in the treatment of scleritis

Drug	Mechanism	Dosages/Route	Side Effects
<i>Anti-TNF Agents</i>			
Etanercept	Dimeric fusion protein between Fc portion of IgG1 and soluble TNF receptor	25 mg two times/week or 50 mg SC once a week	Opportunistic infection, reactivation of TB, malignancy, demyelinating disease, uveitis
Infliximab	Chimeric monoclonal antibody to TNF- α	3–10 mg/kg IV Q4–8 weeks	Opportunistic infection, reactivation of TB, malignancy, lupus-like syndrome, CHF exacerbation
Adalimumab	Humanized IgG1 antibody to TNF- α	20–40 mg SC Q1–2 weeks	Opportunistic infection, reactivation TB, increased malignancy, lupus-like syndrome, CHF exacerbations
<i>Anti B-Cell Therapy</i>			
Rituximab	Chimeric antibody to CD20	500–1000 mg IV Q2 weeks $\times$ 2, then repeat Q6 to 18 months	Infusion reaction, PML, SJS, opportunistic infection

SC: subcutaneous; TNF: tumor necrosis factor; TB: tuberculosis; CHF: congestive heart failure; PML: progressive multifocal leukoencephalopathy; SJS: Stevens Johnson Syndrome