

# Role of Topical Cyclosporin in Scleritis: A Case Series

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**Purpose:** To report on a series of cases of anterior, non-necrotizing scleritis, that were effectively treated with topical 0.075% - 1% cyclosporine A and to provide a literature review on other treatment modalities of this condition.

**Material and Methods:** This study includes eleven consecutive patients of acute anterior, non-necrotizing scleritis reporting to Mughal eye hospital, Lahore, during January to December 2012. There were 7 females and 4 males between the age 18 and 65 years. They all had mild to moderate, anterior scleritis, nodular in 6 cases and diffuse in 5 cases. All patients were thoroughly investigated regarding auto-immune disorders. Only 2 cases had associated rheumatoid arthritis. They were treated with topical cyclosporine and preservative-free artificial tears for 2-3 months and followed-up for 1 year regarding recurrence.

**Results:** All patients showed a favorable response to treatment. The scleritis score improved remarkably within 2 weeks of Cyclosporin therapy. The symptoms flared up in only 2 out of 11 cases (18%) when they abruptly stopped therapy. All cases remained asymptomatic over the one year follow-up after stopping treatment.

**Conclusion:** Topical 0.075% - 1% Cyclosporine A is a safe and effective long-term treatment of anterior scleritis of mild to moderate severity. It should be considered as a steroid-sparing agent, particularly in recurrent disease and in those patients who experience adverse effects of systemic medications.

Scleritis is a severe, potentially sight threatening, inflammatory disease involving the ocular surface. It has been classified by PG Watson et al,<sup>1</sup> into anterior and posterior. Anterior scleritis can be diffuse, nodular, necrotizing with inflammation (necrotizing), and necrotizing without inflammation (scleromalacia perforans). Posterior scleritis<sup>2</sup> is characterized by flattening of the posterior aspect of the globe, thickening of the posterior coats of the eye (choroid and sclera), and retrobulbar edema. The author states that the anatomical site and clinical appearance of the disease at presentation reflected its natural history; majority of patients remain in the same clinical category throughout the course of their disease. Diffuse anterior scleritis had a lower incidence of visual loss (9%) than either nodular scleritis (26%)

or necrotizing disease (74%), Patients with necrotizing scleritis were older than patients in the other groups and more frequently had an associated systemic disease than patients with either diffuse or nodular disease, 57%.<sup>3</sup> According to another study, necrotizing scleritis is associated with rheumatoid arthritis in most cases and less often with SLE, Crohn's disease, Behcet's disease and gout.<sup>4</sup> Diffuse and nodular anterior scleritis is less often associated with any systemic disease.

An underlying infectious etiology has been found to be relatively less common. According to a study by Gonzalez et al<sup>5</sup>, out of 500 patients presenting with scleritis, only 9.4% had an underlying infection with Herpes virus infection (74%), tuberculosis (10%) and other infections in the remaining 14%.

An autoimmune deregulation in a genetically predisposed host is presumed to cause scleritis. Inciting factors may include infectious organisms, endogenous substances, or trauma. The inflammatory process may be caused by immune complex-related vascular damage (type III hypersensitivity) and subsequent chronic granulomatous response (type IV hypersensitivity).<sup>6</sup>

Ocular complications of scleritis, which cause visual loss and eye destruction, appear as a result of the extending scleral inflammation. These include peripheral ulcerative keratitis (13 - 14%), uveitis (about 42%), glaucoma (12 - 13%), cataract (6 - 17%), and fundus abnormalities (about 6.4%).<sup>7</sup> They are most common in necrotizing scleritis, the most destructive type of scleritis.

Despite recent advances, its treatment remains a difficult problem. Systemic immunosuppressive therapy with corticosteroids or immunosuppressive agents or both is usually required to control the disease. Early therapeutic intervention is important to prevent ocular complications and to minimize the potential morbidity and mortality associated with underlying systemic disease. Systemic corticosteroids in high dosage, either topical orally or in intravenous pulses, are widely accepted as an effective form of treatment in patients with severe scleritis.<sup>8</sup> But this treatment is often associated with unacceptable side effects and does not always control scleral inflammation. Side effects include adrenal suppression, vertigo, psychosis, pseudotumour cerebri, acne, osteoporosis, myopathy and delayed wound healing.

The addition of immunosuppressive agents in patients with severe scleritis improves the ocular outcome and decreases the morbidity associated with systemically administered corticosteroids.<sup>9</sup> Azathioprine, cyclophosphamide, and cyclosporine have previously been reported to be effective and safe in the management of severe ocular inflammation.<sup>10</sup>

Various studies have reported the successful use of topical cyclosporine in the treatment of patients with a variety of ocular inflammatory syndromes resistant to other immunosuppressive regimens.<sup>11,12</sup> Evidence obtained from these studies supports the efficacy of topical cyclosporine treatment through its immunomodulatory action, reversing inflammation of the ocular surface and lacrimal glands. In the present study we report the therapeutic effect of topical cyclosporine in the treatment of mild to moderate scleritis.

## MATERIAL AND METHODS

This is a prospective case series of eleven consecutive patients with scleritis who attended the out patients department of Mughal eye hospital, Lahore, from January to December 2012. All cases were assessed by the same ophthalmologist. A detailed history was taken and physical examination performed; distinction was made between episcleritis and scleritis by the presence of eye pain, local tenderness over the area of nodule in 6 cases and diffuse purplish hue in 5 cases of scleritis; the conjunctiva could be freely moved over that area and no blanching of the lesion was achieved by a drop of 10% phenylephrine eye drops. The cases presenting with episcleritis were excluded from the study. All patients were graded to have an active anterior non-necrotizing scleritis of mild to moderate severity without associated anterior or posterior uveitis. Appropriate investigations including CBC, ESR, Rh - factor, serum ANCA, ACE, chest X-ray and Mantoux test to exclude the presence of an associated auto-immune or infectious disease; HLA auto-antibodies and C Reactive Protein testing was not done due to economic constraints.

The clinical features of the patients are summarized in (Table 1). There were seven females between ages of 18 - 65 years and four males with the age of 45 years. A subjective grading system, analogous to that previously described for patients with uveitis and retinal vasculitis was used (Table 2).<sup>13</sup> A scleritis score was calculated when the patients first presented, then at each follow-up visit and at the end of the study (Table 3). Improvement was defined as a decrease in the total score of greater than 2 and resolution at a total score of less than or equal to 4.

All patients were fully informed regarding the proper use and expected side-effects of topical cyclosporine which was then started as 1% twice /day (freshly prepared from cyclosporin capsules, 50 mg BIORAL; the water-miscible gel from 2 capsules mixed with 5cc distilled water) along with preservative - free artificial tears 4 x / day (Biolan gel from Stullin Pharma, Germany). Treatment was started and patients were reviewed weekly to note their subjective and objective improvement. The therapy was continued for 2 months in mild cases (Scleritis score 6 - 7) and 3 months in moderate cases (Scleritis score = > 8). Then it was gradually tapered by reducing the strength of Cyclosporin drops to 0.075%, twice daily for 1 week, then once daily for one week, then on alternate day for a week and then it was finally stopped.

**Table 1:** Characteristics of patients included in study

Characteristic	Scleritis n (%)
<b>Person Specific Characteristics</b>	
No. of Patient	11
Age: 18 - 39 years	8
Age: 40 - 54 years	1
Age: 55 - 65 years	2
Gender, Female	7 (63)
Gender, Male	4 (36)
Duration of Inflammation (years)	1 month
Systemic (Extra ocular) autoimmune Disease	2 (28.5)
Bilateral Inflammation	4

**RESULTS**

Associated active rheumatoid arthritis was found in only 2 female cases who were 60 years old. No other systemic auto-immune or infectious disease was present in any other case.

In all cases, the subjective improvement of eye pain was noted in the first week of therapy and objectively, reduction in scleral injection and tenderness improved within 2 weeks of therapy. The scleritis scoring system is detailed in Table 2, and Table 3 summarizes the scleritis score for each patient at presentation and at four weeks after the commencement of treatment. In all patients there was a significant decrease in the scleritis score at four weeks. This decrease in the scleritis score was maintained over the subsequent observation period. None of the cases developed scleral thinning, uveitis or a raised IOP during or after the termination of therapy. The mean duration of treatment was 2 months in mild cases and 3 months in moderately severe cases. No recurrence of scleritis was noted in 9 cases after stopping the therapy. Two cases (18%) stopped therapy abruptly after one month only; in

**Table 2:** Scoring system for severity of scleritis

Clinical Feature	Clinical Grading	Score	No. of Cases
Location	Unilateral	1	Unilateral = 7 cases
	Bilateral	2	Bilateral = 4 cases
Tenderness	0 - 4 +	0 - 4	Grade 3 = 9 cases
			Grade 4 = 2 cases
Nodule	Single	2	Single = 6 cases
	Multiple	4	Diffuse = 5 cases
Scleral necrosis	Absent / quiescent	0	2 cases, present
	Present	2	
	Progressive	4	
Visual acuity	Initially < 6 / 12, or decreased 2 or more lines	1	All had 6/6 vision
Anterior chamber cells	0 - 4 +	0 - 4	0
Raised IOP	> 22 mmHg	1	0
Vitreous cells	0 - 4 +	0 - 4	0
Retinal detachment	Absent	0	0
	Present	4	

**Table 3:** Scleritis score in patients undergoing treatment

No. of Patients	Pre-treatment Score	Score at End of Study
6	9	2
5	7	1

**Table 4:** Side effects of topical cyclosporin

Side Effect Studied	No. of Patients
Ocular burning	4
Conjunctival hyperemia	0
Discharge	0
Epiphora	0
Eye pain	0
Pruritus	0
Foreign body sensation	1

them, scleritis re-appeared which was again successfully controlled by starting the same therapy and educating them regarding their proper use and weaning. No recurrence of symptoms was noted in any case over one year follow-up after stopping the therapy.

Cyclosporin eye drops were well tolerated by all patients. Table 4 summarizes the side effects looked for in the study. The only problem noted was stinging and a burning sensation on instillation of drops which subsided after instilling preservative-free tear drops after 10 minutes of instillation of cyclosporin eye drops. No other side effect was noted.

## DISCUSSION

All eleven patients included in the study responded to the use of cyclosporine (freshly prepared at our hospital pharmacy). A subjective improvement of eye pain was noted within one week following the start of therapy and improvement of scleral injection and tenderness was noted after two weeks of therapy.

It has been increasingly recognized as an effective therapeutic agent in the management of a variety of autoimmune diseases. It has been effectively used topically in ocular surface disorders like vernal keratoconjunctivitis, dry eye syndrome. Inflammatory

eye disease, particularly uveitis, is often well controlled by the regular use of systemic cyclosporin<sup>14</sup>.

Cyclosporin represents the prototype of a new class of drug that appears to work, at least in part, by acting at the level of cytokine production by immune cells.<sup>15</sup> The selective ability of cyclosporine to interfere with the action of interleukin-2 makes it an appropriate agent for the treatment of diseases mediated by T cells. Although the immune-pathogenesis of scleritis is not fully understood, it is believed to be due to immune complex mediated vascular damage to scleral vessels, with the subsequent generation of a granulomatous reaction. T cells have an essential role in the formation of such granulomas, and cyclosporine may act in part by decreasing this component of the inflammatory response.

Multiple studies on the efficacy of topical cyclosporine for treating inflammatory ocular surface disorders have consistently shown a beneficial effect of the drug.<sup>14,17</sup> The immune-pathogenic mechanism is complex and involves an IgE mediated immediate hypersensitivity response as well as a T cell mediated immune reaction. Animal studies have shown that Cyclosporin has no intraocular penetration; it concentrates on the ocular surface which enhances its anti-inflammatory effect after long term use. Even after a year of regular topical therapy, none to minimal blood concentration and in aqueous taps was found in rabbits.

A large study<sup>16</sup> of 392 patients with non-infectious anterior scleritis highlighted various therapeutic options available included NSAIDs, particularly cox-2 inhibitors (but they result in cardiovascular side effects) in 144 (36.7%), oral or topical steroids in 29 (7.4%), immune modulatory drugs (systemic cyclophosphamide, azathioprine, methotrexate) in 149 (38.0%), biologic response modifiers (BRM) in 56 (14.3%), and none (N = 14). Patients with idiopathic diffuse or nodular scleritis with a low degree of scleral inflammation or without ocular complications may respond to NSAIDs. Patients with idiopathic diffuse or nodular scleritis with a high degree of scleral inflammation may respond to steroids. Patients with diffuse or nodular scleritis with associated systemic disease may respond to IMT or BRMs. Patients with necrotizing scleritis may respond to IMT, mainly alkylating agents.

All these systemic therapies are associated with many side effects. Similarly, topical steroids potentiate

corneo-scleral thinning, raised intra-ocular pressure and cataract. In comparison, topical cyclosporin has minimal side-effects. Only precaution to be used is that the beneficial affect is achieved after two weeks of therapy but the immune process is still active and the therapy has to be continued for at least two months and then gradually tapered, otherwise the disease flares up if treatment is stopped abruptly and too early as seen in our two cases.

## CONCLUSION

This study highlights the fact that topical cyclosporine is a potentially useful drug in the treatment of mild to moderate anterior scleritis; subjective and objective clinical improvement is achieved within 2-3 weeks of regular usage. Hence, it is an effective steroid- sparing agent. Unfortunately, its use is complicated by frequent, mild side effects, like burning and stinging for a short while after instillation of eye drops and may be associated with recurrence of disease on suddenly stopping the therapy.<sup>14</sup> Patients need to be informed and educated regarding its appropriate use.

To avoid recurrence of the disease, therapy has to be continued for at least 2 – 3 months and then gradually tapered. Another problem with cyclosporine eye drops is that they have to be made fresh, without preservatives and have a shelf life of one week only. Despite these limitations we consider that topical cyclosporine is a useful drug in the management of mild to moderate scleritis, and has a high therapeutic value in the treatment of this disease.

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