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ORIGINAL RESEARCH

Outcomes of Escalating Immunosuppressive Treatments for Recalcitrant Noninfectious Posterior Scleritis

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ABSTRACT

Introduction: This article aimed to summarize the outcomes of escalating immunosuppressive treatments for patients with recalcitrant noninfectious posterior scleritis (PS).

Methods: Clinical records of 16 patients diagnosed with recalcitrant noninfectious PS in the Ocular Immunity and Uveitis Department of Zhongshan Ophthalmic Center from September 2016 to December 2021 were reviewed. Patients were treated with escalating immunosuppressive regimen including corticosteroid, immunosuppressants (IMTs), and adalimumab (ADA). Demographic characteristics and clinical findings at each visit were recorded. The doses of prednisone were analyzed. Main outcomes were corticosteroid-sparing effects, control of inflammation, visual acuity, and safety profile.

Results: Ocular pain was the most common finding (100%), followed by the T sign on the B scan (93.8%) and associated anterior scleritis (75.0%). The average initial dose of prednisone was 25.0 mg/day, and tapered to 11.3 and 5.0 mg/day at month 1 and 3, respectively, with statistical significance ($p < 0.05$). The median overall periods of prednisone tapering to 10, 5, and 0 mg/day were 1.0, 3.0, and 3.0 months, respectively. There were 93.8% of patients receiving prednisone $\leq$ 10 mg/day and 68.8% of patients off prednisone at last visit. There were 80% of patients treated with IMT and ADA off prednisone at last visit, reaching the highest percentage compared with others. A best-corrected visual acuity of 1.0 or better at last visit was achieved in 10 eyes (62.5%). The escalating treatments showed good safety profile.

Conclusion: Patients of recalcitrant noninfectious PS benefited from escalating immunosuppressive treatments with favorable visual outcome, in which methotrexate, ciclosporin, and ADA were preferred with good safety.

Keywords: Recalcitrant noninfectious posterior scleritis; Escalating immunosuppressive treatments; Methotrexate; Ciclosporin; Adalimumab; Outcomes

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Key Summary Points

What was known?

The treatment outcomes of patients with recalcitrant posterior scleritis suffering from high risk of visual loss and severe discomfort are commonly unsatisfactory because of a lack of therapeutic option guidelines.

Escalating immunosuppressive treatments are being recognized as new options for ocular immune-inflammatory diseases including posterior scleritis.

What this paper adds?

Escalating immunosuppressive treatments could provide therapeutic benefit with excellent corticosteroid-sparing effects and favorable visual outcome for patients with recalcitrant noninfectious posterior scleritis; methotrexate, ciclosporin, and adalimumab could be preferred among these treatments.

Escalating immunosuppressive treatments should be recommended for recalcitrant noninfectious posterior scleritis.

INTRODUCTION

Scleritis is the inflammation of the sclera, the tough white fibrous outer envelope of tissue covering all of the eyeball except the cornea. Scleritis can be generally classified into two categories according to anatomic distribution: anterior scleritis and posterior scleritis (PS) [1]. PS is a fairly rare form which has been reported to account for only 2–12% of all scleritis cases, among which most are noninfectious type [2–10]. The diagnosis of posterior noninfectious scleritis can be elusive and overlooked because of its various clinical manifestations without specific characteristics, such as ocular redness, pain, visual loss, and so on. It has been demonstrated that patients with PS are at high risk of visual loss [8].

The treatment for PS is still a big challenge for ophthalmologists because of a lack of treatment regimen guidelines. Although corticosteroid is the first-line option for PS in clinic, its potential side effects limit its long-term use. Moreover, the relapse rate ranges from 30% to 80% [2, 7, 11]. Some patients are even resistant to corticosteroid with persistent scleral inflammation or they could not taper doses of corticosteroid successfully [2, 12]; these are considered as recalcitrant patients. Pediatric PS cases are also widely accepted as refractory to traditional options of corticosteroid and aggressive immunosuppressive therapy has been advocated for them [2]. The current status of treatment for these recalcitrant noninfectious PS cases is unsatisfactory. Escalating immunosuppressive treatments are being recognized as new options for different ocular immune-inflammatory diseases including PS. Moreover, corticosteroid-free clinical remission has been the ultimate goal in treating various immune-inflammatory diseases [13–16]. Up to now, few research studies reported the outcomes of escalating immunosuppressive treatments for recalcitrant PS cases, especially corticosteroid-sparing efficacy [6, 17].

The current study was designed to analyze the outcomes of escalating immunosuppressive treatments for recalcitrant noninfectious PS cases, including corticosteroid-sparing effects, control of scleral inflammation, and recurrences during treatment. In addition, we aim to summarize the clinical characteristics, systemic adverse events, and ocular complications.

MATERIALS AND METHODS

Patient Selection and Study Design

This is a retrospective, longitudinal case series. Clinical records of patients diagnosed with posterior scleritis in Zhongshan Ophthalmic Center from September 2016 to October 2021 were reviewed. Diagnostic criteria proposed by Watson and Hayreh [1] combining clinical findings with posterior scleral thickening

demonstrated by B scan ultrasonography were applied in this study. This research was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Zhongshan Ophthalmic Center Research Ethics Committee.

Of the patients with PS, adults without any previous systemic treatment or confirmed with infectious causes were excluded. Adult patients who were not adequately controlled with corticosteroid alone or relapsed after reduction of the oral corticosteroid dose to less than 10 mg/day prednisone and all the pediatric patients with PS were considered as recalcitrant patients, of which those who underwent escalating immunosuppressive treatments (IMT) for at least 3 months with sufficient and detailed clinical records were finally included.

Demographic characteristics of patients were collected, including age at diagnosis, gender, unilateral or bilateral, duration before adding escalating immunosuppressive treatments, and associated systemic rheumatologic diseases including rheumatoid polyarthritis, granulomatosis with polyangiitis, systemic lupus erythematosus, ankylosing spondylitis, sarcoidosis, inflammatory bowel disease, psoriatic arthritis, Sjogren's syndrome, and so on. Clinical outcomes regarding visual acuity, intraocular pressure, and concurrent findings, namely ocular pain, anterior scleritis, degree of anterior sclera inflammation, the T sign on the B scan, swollen optic disc, serous retinal detachment, subretinal localized granuloma, uveitis, macular edema, and peripheral keratitis, were all recorded at each follow-up. Both B scan and standard optical coherence tomography (OCT) in all patients were performed at first presentation and during the follow-up when needed. Fluorescein angiography, computed tomography, or magnetic resonance imaging scan of the orbit was done in suitable patients when needed. Previous and current treatment details of doses and periods of corticosteroid and other concomitant immunosuppressive regimen were also obtained. Systemic side effects, ocular complications, and recurrences were also documented.

Laboratory testing generally included full blood count, renal and liver functions, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody (ANA), anti-double-stranded DNA antibody, antineutrophil cytoplasmic antibody (ANCA), and rheumatoid factor. Systemic infections including hepatitis B, syphilis, tuberculosis, and human immunodeficiency virus were routinely screened and were excluded if positive.

Escalating Immunosuppressive Treatments

Escalating systemic immunosuppressive treatments for enrolled adult patients with duration less than 12 months were oral prednisone plus methotrexate; and treatments for adult patients with duration more than 12 months or concomitant associated systemic disorders were oral prednisone plus methotrexate (MTX), and cyclosporine (CsA) or adalimumab (ADA) were also added; and treatments for pediatric cases diagnosed before 2019 were oral prednisone plus MTX and CsA; and for pediatric cases diagnosed after 2019, treatments were MTX plus ADA with or without prednisone because ADA was permitted in our hospital in 2019. Oral prednisone was started at initial dose of 0.3–0.6 mg/kg/day and tapered fast after other escalating immunosuppressive regimen worked and stopped as soon as possible with controlled sclera inflammation. MTX was usually prescribed at a weekly oral dose of 10–15 mg and CsA was taken at doses of 50–100 mg twice a day.

Main Outcome Measures

Main outcome measures were corticosteroid-sparing effects, control of scleral inflammation, visual acuity, and safety profile. Corticosteroid-sparing effects were analyzed according to the following three aspects: the doses of prednisone at four indicated time points (months 0, 1, 3, and the last visit), the periods of prednisone tapering to 10, 5, and 0 mg prednisone/day, and the percentages of patients with doses less than or equal to 10 mg prednisone/day, 5 mg prednisone/day, or corticosteroid-free at the aforementioned four indicated time points. Degree of scleral inflammation was defined and

documented according to the standard evaluation criteria from 0 to 4; this finding was documented by drawings, photography, or both [18]. Ocular pain was graded as none, mild, moderate, and severe reported by the patient [19]. Control of sclera inflammation was defined as degree of scleral inflammation up to 0.5+ and degree of ocular pain up to the mild level. Recurrence was identified either by relapse of inflammation by a clinical ophthalmologist or by acute ocular symptoms reported by patients. For bilateral patients, the right eye was chosen as the study eye.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 7 software (GraphPad Software, San Diego, CA, USA). *p* values less than 0.05 were considered statistically significant. Continuous variables are presented as the median and interquartile range (IQR). Differences were tested with non-parametric test.

RESULTS

Patient Characteristics

Medical records of 59 patients diagnosed with PS in Zhongshan Ophthalmic Center from September 2016 to December 2021 were reviewed. Sixteen patients with recalcitrant noninfectious posterior scleritis and detailed clinical records were included in this study. The demographic characteristics and clinical findings of these patients at presentation are shown in Table 1. The median age was 24.5 years and 10 (62.5%) patients were female. Twelve (75%) patients were unilateral and three patients were identified with associated systemic disease by a rheumatologist. The median duration before escalating immunosuppressive treatments was 9 months. Ocular pain (100%) was the most common symptom, and 62.5% of cases suffered from severe ocular pain. The T sign on the B scan was observed in 15 eyes (93.8%). Twelve eyes (75.0%) were accompanied by associated anterior scleritis, whose degrees of scleral inflammation were all at least 2+. Swollen optic disc, visual loss, serous retinal detachment, and uveitis were also common in 10 (62.5%), 10 (62.5%), 11(55%), and 8 (50.0%) eyes, respectively. Scleral nodules, ocular hypertension,

Table 1 Demographic characteristics and clinical findings before treatment

Variables (n = 16)	Values
Age (years) (median, IQR)	24.5 (16.8–35.8)
Sex	
Female	10 (62.5%)
Male	6 (37.5%)
Unilateral	12 (75.0%)
Associated systemic disease	3 (18.8%)
Duration before treatment* (month) (median, IQR)	9 (1–12)
Ocular pain	
Mild	0 (0.0%)
Moderate	6 (37.5%)
Severe	10 (62.5%)
Associated anterior scleritis	12 (75.0%)
Degree of anterior scleral inflammation $\geq 2+$	12 (75.0%)
T sign on the B scan	15 (93.8%)
Swollen optic disc	10 (62.5%)
Serous retinal detachment	8 (50.0%)
Subretinal localized granuloma/scleral nodules	2 (12.5%)
Uveitis	8 (50.0%)
Macular edema	1 (6.3%)
Ocular hypertension (> 21 mmHg)	2 (12.5%)
Peripheral keratitis	1 (6.3%)
Visual loss	10 (62.5%)

Treatment was defined as escalating immunosuppressive treatment

Table 2 Corticosteroid-sparing effects

	Overall (*n* = 16)	**Oral prednisone + MTX (*n* = 7)**	**Oral prednisone + MTX + CsA (*n* = 4)**	**Oral prednisone + ADA + IMT (*n* = 5)**
Dose of prednisone, mg/day, median (IQR)				
Initial dose	25.0 (16.3–33.8)	30.0 (20.0–35.0)	17.5 (11.3–27.5)	20.0 (7.5–60.0)
Month 1	11.3 (5.0–20.0)*	20.0 (12.5–20.0)*	7.5 (5.0–10.0)	5.0 (0–22.5)
Month 3	5.0 (0–10.0)*	10.0 (5.0–10.0)*	2.5 (0–5.0)	0.0 (0–15.0)
Last follow-up	0.0 (0–4.4)*	0.0 (0–5.0)*	1.3 (0–4.4)	0.0 (0–11.3)
Period, months, median (IQR)				
10 mg prednisone/day	1.0 (0.5–2.5)	2.5 (2.0–3.0)	0.8 (0.1–1)	0.3 (0–1.6)
5 mg prednisone/day	3.0 (1.0–4.3)	4.5 (2.6–5.3)	2.5 (1.3–3.0)	0.7 (0–2.5)
0 mg prednisone/day	3.0 (2.0–12.0)	10.0 (4.0–19.0)	2.5 (2.0–3.0)	1.0 (0–7.0)
	Baseline	**Month 1**	**Month 3**	**Last visit**
No. of patients, *n* (%)				
Prednisone ≤ 10 mg/day	2 (12.5%)	8 (50.0%)	14 (87.5%)	15 (93.8%)
Prednisone ≤ 5 mg/day	1 (6.3%)	4 (25.0%)	8 (50.0%)	14 (87.5%)
Prednisone-free	1 (6.3%)	2 (12.5%)	6 (37.5%)	11 (68.8%)
	Overall (*n* = 16)	**Oral prednisone + MTX (*n* = 7)**	**Oral prednisone + MTX + CsA (*n* = 4)**	**Oral prednisone + ADA + IMT (*n* = 5)**
No. of patients at last visit, *n* (%)				
Prednisone ≤ 10 mg/day	15 (93.8%)	7 (100.0%)	4 (100.0%)	4 (80.0%)
Prednisone ≤ 5 mg/day	14 (87.5%)	6 (85.7%)	4 (100.0%)	4 (80.0%)
Prednisone-free	11 (68.8%)	5 (71.4%)	2 (50.0%)	4 (80.0%)

Statistical significance was calculated in comparison with initial dose in each group by paired Wilcoxon signed rank test

*$p < 0.05$ indicates statistical significance

Table 3 Outcomes of escalating immunosuppressive treatments at last visit

Outcome	No. of eyes	Percentage (n = 16)
BCVA		
1.0 or better	10	62.5%
0.6–0.8	2	12.5%
0.2–0.5	4	25.0%
Degree of anterior scleral inflammation		
0	11	68.8%
0.5	4	25.0%
1	0	0.0%
2	1	6.3%
Ocular pain		
None	9	56.3%
Mild	7	43.8%
Moderate	0	0.0%
Severe	0	0.0%
Ocular hypertension (> 21 mmHg)	0	0.0%
T sign on the B scan	0	0.0%

macular edema, and peripheral keratitis were relatively rare.

Efficacy

The corticosteroid-sparing effects are presented in Table 2. The median initial dose of prednisone was 25.0 mg per day, and the doses were tapered to 11.3 and 5.0 mg per day at month 1 and month 3, respectively, with statistical significance ($p < 0.05$) compared to initial dose. The median dose of prednisone at the last visit was reduced to 0 mg per day with statistical significance ($p < 0.05$) compared to the initial dose. In the subgroup analysis, doses of prednisone were tapered in a rapid manner in all three subgroups with different treatments. The median periods of corticosteroid tapering to 10, 5, and 0 mg per day are summarized as 1 month, 3 months, and 3 months respectively. It is noted that the shortest periods of tapering to 10 mg/day (0.3 month), 5 mg/day (0.7 month), and 0 mg/day (1.0 month) all occurred in the subgroup patients receiving prednisone + ADA + IMT. The results also present percentages of patients with 10, 5, and 0 mg/day prednisone at four indicated points, which increased as time went by. Overall, 11 (68.8%) patients got rid of prednisone at last visit and the highest percentage of 80% was reached in the subgroup of patients receiving prednisone + ADA + IMT.

Table 3 shows the outcomes of study eyes at last visit. A best-corrected visual acuity (BCVA) of 1.0 or better was achieved in 10 eyes (62.5%). All the eyes had a low degree of anterior scleral inflammation ≤ 2, of which 68.8% of eyes (n = 11) were completely recovered. None of them suffered from severe ocular pain and 9 eyes (56.3%) even manifested without ocular pain. Moreover, the T sign was relieved in all patients.

Table 4 summarizes the treatment regimens, follow-up periods, and recurrences. The median follow-up period was 11 months and ranged from 4 to 48 months. There were 17 recurrence episodes in total during the whole follow-up and eight patients (50%) experienced recurrence. Nine recurrences (53%) occurred in four patients (80%) receiving prednisone + MTX + CsA, which ranked the highest, and two episodes occurred in only one patient (20%) in the subgroup with ADA, which ranked the least.

Safety

Systemic adverse events and ocular complications were recorded during the whole treatment period and follow-ups (Table 5) and no serious adverse event was observed. Three patients experienced temporary gastrointestinal (GI) upset and were successfully treated with gastric acid suppression. One patient had mildly elevated liver enzymes and received guard liver therapy. Two patients treated with MTX

Table 4 Escalation of systemic immunosuppressive treatment of the 16 patients

Patient no.	Previous treatment	Escalation of systemic treatment	Follow-up period (months)	Recurrences (number)
1	IV + oral prednisone	Oral prednisone, methotrexate	28	0
2	Oral prednisone	Oral prednisone, methotrexate	48	1
3	Oral prednisone, cyclosporine	Oral prednisone, methotrexate, adalimumab	14	0
4	Oral prednisone	Oral prednisone, methotrexate	10	1
5	Oral prednisone	Oral prednisone, methotrexate, cyclosporine	42	4
6	IV + oral prednisone, cyclophosphamide	Oral prednisone, methotrexate, cyclosporine	48	3
7	Oral prednisone + topical corticosteroids	Oral prednisone, methotrexate	10	2
8	IV + oral prednisone, cyclosporine	Oral prednisone, methotrexate, cyclosporine	16	2
9	Oral prednisone + topical corticosteroids	Oral prednisone, methotrexate, cyclosporine, adalimumab	12	2
10	Oral prednisone + topical corticosteroids	Oral prednisone, methotrexate	6	0
11	Topical corticosteroids	Oral prednisone, methotrexate, cyclosporine	12	0
12	Oral prednisone + topical corticosteroids	Oral prednisone, methotrexate	8	2
13	Topical corticosteroids	Methotrexate, adalimumab	7	0
14	Topical corticosteroids	Oral prednisone, methotrexate, adalimumab	5	0
15	Oral prednisone + topical corticosteroids	Oral prednisone, methotrexate, adalimumab	5	0
16	Oral prednisone + topical corticosteroids	Oral prednisone, methotrexate	4	0

Table 5 Systemic adverse events and ocular complications

Systemic side effects	No. of patients	Percentage of patients (n = 16)
GI upset	3	18.8%
Mouth ulcers	0	0.0%
Hair loss	2	12.5%
Elevated liver enzymes	1	6.3%
Bone marrow suppression	0	0.0%
Infection	0	0.0%
Other side effects	0	0.0%
Ocular complications		
Glaucoma	2	12.5%
Cataract	2	12.5%

suffered from mild hair loss. Three patients (18.8%) had ocular complications including glaucoma and cataract, and one of them suffered from both glaucoma and cataract simultaneously.

DISCUSSION

PS is a sight-threatening disease whose current treatment is still clinically unsatisfactory. However, optimal treatments of this disease have been rarely studied. We conducted this retrospective and longitudinal study aiming to optimize the treatment via analysis of the outcomes of escalating immunosuppressive treatments for patients with recalcitrant noninfectious PS. We found that approximately 94% of patients with PS reached controlled scleral inflammation after escalating immunosuppressive treatments with systemic corticosteroids $\leq$ 10 mg and 70% of patients succeeded in tapering off corticosteroid with quiescent status. Our study provides preliminary evidence that escalating immunosuppressive treatments should be recommended for recalcitrant noninfectious PS.

In our case series, 18.8% of patients were identified as having systemic rheumatologic disease, which was a little lower than the proportion in most previous series including adult cases ranging from 29% to 40% [1, 7, 8, 11, 20, 21]. But it is noted that there were four pediatric patients in our case series and it has been reported that no underlying systemic rheumatic disorder was diagnosed in all pediatric patients reported in the literature [2, 22], which could result in the lower percentage of accompanied systemic diseases in our study. However, Foster et al. also showed that 19.4% of patients in their research [3] had accompanying systemic disease, a proportion that was quite similar to ours.

B scan is essential for diagnosing PS, of which the T sign is an important manifestation. The T sign occurs when the thickness of the posterior scleral wall increases and fluid accumulates in the Tenon capsule, which looks like a letter T. In total, 93.8% of our cases manifested with the T sign, which was similar to the proportion of positive cases reported by Chee's group and Okada's group, 90–100% [2, 11]. However, two other research studies showed much lower proportions of 25% and 41%, respectively [7, 23]. This apparent discrepancy may be attributed to the fact that the stage of scleral inflammation in all cases was not absolutely the same. Patients at the onset stage may just manifest as increased scleral wall without fluid in the Tenon capsule permanently. As the disease progresses, the fluid begins to accumulate in the Tenon capsule to form the typical T sign. Patients enrolled in our study had recalcitrant PS, were not in the early stage, and had sufficient time to form the typical T sign. Pediatric cases are commonly regarded as serious and refractory. In Okada et al.'s research, all 13 pediatric cases were demonstrated to have the T sign [2], and the high proportion of T sign we observed (93.8%) may partly result from the four pediatric cases enrolled in our study.

There is indeed a lack of research on optimizing the treatment of recalcitrant noninfectious PS and to explore a better therapeutic option, we applied aggressive

immunosuppressive treatments in 16 patients enrolled in our study. MTX was the most commonly used regimen (100%), followed by CsA (31%) and the same as ADA. Among the limited research studies regarding PS, the application of non-steroidal immunosuppressive regimens included MTX, CsA, MMF, AZA, CTX, and ADA. About 30–85% of patients in these studies received immunosuppressive regimens and MTX was the most frequently prescribed regimen ranging from 20% to 82%, and it showed high efficacy even up to 100% [2, 6, 7, 11, 17]; these findings were partly comparable to ours. But there is a lacking of detailed and accurate results of steroid-sparing effects. The current study is the first time that we have demonstrated that aggressive immunosuppressive treatments for recalcitrant noninfectious PS could bring excellent steroid-sparing effects, in which the doses of prednisone tapered rapidly and 94% of patients tapered to less than 10 mg of prednisone or equivalent as fast as by 1 month and 70% of patients got rid of prednisone within a median period of 3 months. The results showed that aggressive immunosuppressive treatment was quite beneficial for tapering steroid doses in PS. It is notable that the doses of prednisone in patients with additional treatment of CsA tapered faster than that of patients with oral prednisone combined with MTX, which is consistent with previous literature on CsA, and it indicates that CsA can exhibit a faster steroid-sparing effect than other classical immunosuppressive agents including MTX [24, 25]. Moreover, the results of our study enrich the options of escalating immunosuppressive treatments for PS considering the limited literature applying CsA and ADA in PS. It should be pointed out that research studies focusing mainly on PS are in great demand and the majority of previous efforts focused on anterior scleritis, enrolling fewer than ten PS case [6, 17]. It is notable that there were little detailed records in previous research studies specifically for guiding treatment of PS. Our data represents a larger, "purer" patient population with PS.

Okada's group and Cheung's group both reported that recurrences after remission were observed in 60% and 70%, respectively, of patients during the immunosuppressive treatment in their research studies, proportions which were a little higher than ours (50%) [2, 11]. The different choices of immunosuppressive regimen may contribute to the discrepancy, in which non-steroidal immunosuppressive treatments were administered in only 70% and 85% of patients in the two research studies, respectively, proportions both less than ours (100%). We may infer that more aggressive immunosuppressive treatments can reduce the rate of recurrence.

The current study involved the largest sample size focusing on the outcomes of escalating immunosuppressive treatments purely for recalcitrant noninfectious PS. In this study, 75% of patients finally gained a visual acuity $\geq$ 0.6 and 62.5% even completely recovered to visual acuity $\geq$ 1.0. It was much better than McCluskey's report in which 31% of cases had vision loss (loss of vision of 2 or more lines) and 3% of cases were even blind, in which the majority of enrolled cases just obtained treatment with non-steroidal anti-inflammatory drugs [8]. Conversely, Cheung and his colleagues reported favorable visual outcomes of their pediatric cases treated with immunosuppressive agents similar to ours [2]. It can be inferred that inadequate immunosuppressive treatment in the study by McCluskey resulted in their poor visual prognosis. Moreover, no one in our study complained of moderate or severe ocular pain after treatment, and the T sign in all cases was relieved at last visit. As for the safety profile, no one discontinued regimen because of side effects. Our study is the first to reveal overall satisfactory effects of escalating immunosuppressive treatments specifically for recalcitrant noninfectious PS.

There are possible biases and limitations in this study. Firstly, the current study was retrospectively completed. Furthermore, the data were collected from one center and it cannot reflect the entire spectrum of PS in China. Secondly, there is a lack of a matched control group treated with monotherapy with corticosteroid in the absence of other immunosuppressive therapy, which would have the capacity to show the pure result of the tapering effect of steroid. Thirdly, it was a relatively small case

series and the follow-up period was not long enough. Nevertheless, we are confident that this study indeed expands key knowledge in terms of escalating immunosuppressive treatments for recalcitrant noninfectious PS in a Chinese clinical setting. Prospective, multicenter, randomized clinical trials of larger samples are required to further study the effects of escalating immunosuppressive treatment on PS, aiming to optimize the treatment for PS.

CONCLUSION

In total, 94% of patients of recalcitrant noninfectious PS in this case series benefited greatly from escalating immunosuppressive treatments with favorable visual outcomes and control of scleral inflammation; MTX, CsA, and ADA were preferred treatments with good safety properties. Escalating immunosuppressive treatments can not only be conducive to reduce corticosteroid dosage in a rapid manner but can also reach a high rate of controlling scleral inflammation.

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Disclosures. Yuan Pan, Yu-Xi Chen, Yao Lu, Yan-Yan Xie, Yi-Wen Xia and Dan Liang have nothing to disclose.

Compliance with Ethics Guidelines. This research was approved by the Zhongshan Ophthalmic Center Research Ethics Committee (2020KYPJ104) and all procedures adhered to the tenets of the Declaration of Helsinki.

Data Availability. All data are available from the corresponding author upon request.

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