EXTENDED REPORT

The natural history of Stevens–Johnson syndrome: patterns of chronic ocular disease and the role of systemic immunosuppressive therapy

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The case reports are given in Appendix 1 available on the BJO website at <http://bjo.bmj.com/supplemental>

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Objective: To characterize patterns of chronic ocular disease in patients with Stevens–Johnson syndrome (SJS) and its variant toxic epidermal necrolysis (TEN), and to describe their response to treatment.

Methods: Retrospective case series. A review of hospital records of 30 patients (60 eyes) with ocular manifestations of SJS or TEN was carried out. The principal outcome measure was to identify and classify the patterns of chronic ocular disease in SJS and TEN. The secondary outcome measure was the response to treatment.

Results: Patterns of chronic ocular disease observed after the acute episode included: mild/moderate SJS, severe SJS, ocular surface failure (SJS-OSF), recurrent episodic inflammation (SJS-RI), scleritis (SJS-S) and progressive conjunctival cicatrization resembling mucous membrane pemphigoid (SJS-MMP). The median follow-up was 5 years (range 0–29). 19 patients (29 eyes (48%)) developed SJS-OSF, SJS-RI, SJS-S or SJS-MMP during follow-up. SJS-OSF was present in 12 patients (18 eyes (30%)). In 5 patients (eight eyes) this developed 1 year after the acute illness, without any further inflammatory episodes; it was associated with SJS-RI in 1 patient (2 eyes), with SJS-RI and SJS-S in 1 patient (1 eye), with SJS-S in 1 patient (1 eye) and with SJS-MMP in 4 patients (6 eyes). Episodes of SJS-RI occurred in 4 patients (7 eyes (12%)). The median time from acute disease to the first episode of SJS-RI was 8.5 years (range 5–63). SJS-S developed in 2 patients (4 eyes (7%)), of which 2 eyes subsequently developed SJS-OSF. SJS-MMP developed in 5 patients (10 eyes (16.6%)). The median duration from the acute stage to the diagnosis of SJS-MMP was 2 years (range 1–14). Immunosuppressive therapy successfully controlled inflammation in 10/10 patients with SJS-MMP, SJS-RI or SJS-S.

Conclusion: Ocular disease in SJS/TEN is not limited solely to the sequelae of the acute phase illness. Patients and physicians need to know that ocular disease progression, due to surface failure and/or acute inflammatory conditions, may occur at variable periods following the acute disease episode. Recognition of this, and prompt access to specialist services, may optimise management of these uncommon patterns of disease in SJS.

Erythema multiforme major (Stevens–Johnson syndrome) (SJS) is a complex immunological syndrome characterised by acute blistering affecting the skin and at least two mucous membranes. Toxic epidermal necrolysis (TEN) is the most severe form of erythema multiforme and involves >30% of the skin, which sloughs in sheets.

Although severe corneal damage can result from the effects of the acute stage of the disease, it more usually develops as a result of the chronic complications. Corneal damage is the most severe long-term complication for survivors of TEN and SJS.^{1–5}

Little information exists regarding the natural history of chronic ocular disease in SJS. The chronic complications have different aetiologies and may co-exist or occur sequentially in the same patient.⁶ Whereas a subset of patients have mild ocular involvement, other patients present with severe complications early after the acute stage, caused by conjunctival scarring.^{1–5} A major cause of chronic disease is stem cell failure (ocular surface failure in SJS (SJS-OSF)).⁷ Another cause of late sight-threatening complications is recurrent conjunctival inflammation (SJS with recurrent inflammation (SJS-RI)),⁸ not associated with trichiasis, entropion, keratoconjunctivitis sicca or lid margin keratinisation. An ocular mucous membrane pemphigoid picture has also been described in some cases of late SJS (SJS with ocular mucous membrane pemphigoid (SJS-MMP)).⁹ Late diffuse scleritis complicating SJS has also been reported (SJS-S).¹⁰ As the management strategies differ for

these conditions, identification of these infrequently described patterns of late exacerbations in SJS is important to the successful management of this condition.

In this study we identify these different causes of chronic eye involvement in SJS, and the timing of their development, in order to describe the natural history of chronic eye disease in SJS. The outcome of therapies used to manage these causes of chronic eye involvement is described.

PATIENTS AND METHODS

All patients attending Moorfields Eye Hospital (MEH) from 1975 to 2004 with SJS or TEN were identified from the hospital's electronic patient records and from the Cornea and External Disease Service immunosuppression database. The inclusion criterion was patients with a dermatological diagnosis of SJS or TEN and eye involvement. As the ocular manifestations of these diseases are similar,⁵ they are not differentiated in the analysis, and both conditions are referred to as SJS.

The principal outcome measure was the classification of the causes of chronic ocular involvement in SJS. The secondary outcome was the response of these to treatment. For the principal outcome, the different causes of ocular disease were

Abbreviations: MEH, Moorfields Eye Hospital; MMP, mucous membrane pemphigoid; OSF, ocular surface failure; RI, recurrent inflammation; S, scleritis; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis

classified using nomenclature from previous reports and, where our patients developed different disease variants, this has been described. For each patient, each eye was assigned to one of these conditions and, if another cause of disease developed, the date in relation to the onset of disease was recorded. The following classification of disease in SJS was used (fig 1):

- Mild/moderate SJS^{1–6}: mild/moderate sequelae resulting from conjunctival scarring. These were eyes with healthy corneas, no recurrent or progressive inflammation and no progressive conjunctival scarring.
- Severe SJS^{1–6}: severe sequelae resulting mainly from conjunctival scarring. These included eyes with a clinical diagnosis of ocular surface disease, without definitive evidence of stem cell deficiency. Eyes were very dry with an opaque, vascularised and irregular surface, but with a stable epithelium and no evidence of conjunctival inflammation or progressive scarring.
- Ocular surface failure¹¹ (SJS-OSF): surface failure with evidence of stem cell deficiency occurring after the acute episode of SJS. Dysfunction of the stem cells of the corneal epithelium was identified by late fluorescein staining, superficial vascularisation, signs of complete conjunctivalisation or keratinisation of the cornea, an unstable epithelium or cytological evidence of stem cell failure (presence of goblet cells on the corneal surface, and absence of cytokeratin CK3 and presence of cytokeratin CK19 on immunohistochemistry).¹²
- Recurrent inflammation⁸ (SJS-RI): eyes with recurrent episodes of conjunctival inflammation, occurring in the absence of either external aggravating factors or other non-ocular mucosal manifestations of recurrent disease, and without evidence of progressive scarring.
- Scleritis¹⁰ (SJS-S): patients developing scleritis after the acute episode of SJS.
- Mucous membrane pemphigoid (SJS-MMP): eyes with early or late⁹ conjunctival inflammation, not associated with external aggravating factors (such as lid margin disease), and leading to progressive scarring with or without basement membrane antibodies on biopsies.

This study was conducted after approval by the local research governance committee.

Figure 1 Natural history of progression of ocular disease following onset of SJS/TEN.

RESULTS

Thirty patients (10 male and 20 female; median age 38 years (range 12–79)) who had developed SJS (24) or TEN (6) and who had been treated at MEH were included. Drugs were the most common triggering factor (18 cases), with antibiotics implicated in seven cases. An infectious aetiology was identified in nine cases and the precipitating agent was unknown in four of these cases. In two patients, there was both a history of previous drug intake and infection. Immunisation was the precipitating agent in one case. The median follow-up was 5 years (range 0–29). The median age at onset of the initial acute disease was 18 years (range 1–69). The median time from the acute episode to referral was 3 years (range 0–53). Table 1 summarises the study population, their patterns of chronic ocular disease and immunosuppressive treatment used.

Mild/moderate SJS was diagnosed in four patients (cases 1–4, eight eyes) at presentation and remained stable throughout follow up.

Severe SJS was present in seven patients (cases 5–11), in at least one eye, at presentation and remained stable throughout their follow-up.

Severe SJS developed in four patients (cases 12–15), who initially had mild/moderate SJS, but whose disease progressed, in one or both eyes, as a consequence of the chronic effects of surface disease without late acute episodes of inflammation.

SJS-OSF developed in 12 patients (18 eyes) (cases 16–27). Five of these patients (eight eyes, cases 16–20) developed late surface failure, without any acute episodes of inflammation, between 1 and 2 years after the onset of the acute episode of SJS/TEN; cases 17 and 20 (three eyes) had had minimal corneal disease immediately after recovery from the acute phase of SJS/TEN. Three patients (four eyes, cases 21–23) developed SJS-OSF following inflammation due to SJS-RI (case 21), both SJS-RI and SJS-S (case 22), and SJS-S (case 23 and fig. 2).

SJS-RI episodes developed in four patients (seven eyes) during their follow-up, cases 21 and 22 described above who also developed SJS-OSF and cases 29 and 30 who had no other late complications of the disease. Three of these eyes (cases 29 and 30) had been classified as mild/moderate SJS when seen for the first time at MEH. The time from the acute disease to the first episode of recurrent inflammation in these cases was 5, 8, 63 and 9 years, respectively (median 8.5 years).

SJS-MMP developed in five patients (10 eyes) with either mild/moderate or severe SJS (cases 24–28 and fig.3). The median time from the acute stage to the diagnosis of SJS-MMP was 2 years (range 1–14 years). In four cases (24–27) (six eyes) SJS-OSF also developed.

Conjunctival biopsy, for routine histopathology and direct immunofluorescence, was carried out in seven patients (cases 4, 13, 16, 22, 25, 27 and 30). Biopsy results were normal in five patients. In case 27 there was an inflammatory infiltrate along the epithelial–stromal margin, and immunofluorescence showed immunoglobulin (Ig)M, IgG and C3 staining at the conjunctival basement membrane, consistent with the development of ocular mucous membrane pemphigoid. In case 13, the conjunctival biopsy showed granular complement deposition, consistent with SJS-associated conjunctivitis.⁸

Immunosuppression was initiated with both systemic corticosteroids and a steroid-sparing immunosuppressive agent. The corticosteroids were tapered and stopped once the inflammation was brought under control. Immunosuppressive therapy successfully controlled inflammation in 10 patients (see table 1). In case 4, the patient had been prescribed oral prednisolone and dapsone in the first year after the acute episode, before the first visit to MEH; however, there had been little or no response. When she first attended MEH her disease was classified as mild and she did not require immunosuppression. Immunosuppressive therapy

Table 1 Summary of the study population and patterns of chronic ocular disease

Dates of diagnosis of complications of SJS												
Case no. DOB Sex	Year of onset	Follow-up dates	Eye	Mild/ moderate SJS	Severe SJS	Surface failure	SJS-MMP early/late	SJS-RI	SJS-S	VA first	VA last	Systemic immunosuppression
Patients with mild/moderate SJS at first and last follow-up												
1. 1968 F	SJS 1993	1997–2004	OD	1997–2004						6/9	6/9	
			OS	1997–2004						6/6	6/9	
2. 1980 M	SJS 1991	1992 One visit	OD	1992						6/6		
			OS	1992						6/6		
3. 1971 M	SJS 2000	2001–2004	OD	2001–2004						6/6	6/5	
			OS	2001–2004						6/5	6/9	
4. 1970 F	SJS 2003	2004 One visit	OD	2004						6/6		Prednisolone 2003–2004, Dapsone
			OS	2004						6/6		
Patients with severe SJS (in at least one eye) at first and last follow-up without any late complications of SJS												
5. 1944 F	TEN 1992	1994–2004	OD		1994–2004					6/36	6/36	
			OS	1994–2004						6/9	6/18	
6. 1958 F	SJS 1997	2000–2004	OD		2000–2004					6/60	CF	
			OS		2000–2004					6/60	6/24	
7. 1975 M	SJS 1976	1998–2003	OD		1998–2003					CF	1/60	
			OS	1998–2003						6/9	6/9	
8. 1963 M	SJS “as child”	1999–2004	OD		1999–2004					6/60	CF	Dapsone 1999–2004, Ciclosporin 2002
			OS		1999–2004					6/36	6/24	
9. 1925 F	SJS 1957	1975–2004	OD		1975–2004					6/36	HM	
			OS	1975–2004						6/12	6/12	
10. 1936 F	SJS 1969	2000–2004	OD	2000–2004						6/9	6/6	
			OS		2000–2004					HM	6/60	
11. 1945 F	SJS 1948	2001–2004	OD		2001–2004					6/18	6/18	
			OS		2001–2004					6/36	6/60	
Patients who developed severe SJS in one or both eyes after the first visit without a late inflammatory complication of SJS												
12. 1954 F	SJS 1960	1999–2004	OD	1999	2001–2004					6/18	6/12	
			OS		1999–2004					HM	2/60	
13. 1965 M	SJS 1972	1995–2003	OD	1995–2003						6/9	6/6	Prednisolone
			OS	1995	1998–2003					6/12	CF	
14. 1956 F	SJS 1965	1995–2004	OD	1995–2004	1998*					6/18	6/12	
			OS	1995–2004						6/6	6/6	
15. 1961 M	SJS 1982	1982–2003	OD	1995–1999	1982–1995*; 2000–2003 1982–2003					6/24	6/12	
			OS							CF	6/36	
Patients developing surface failure without late inflammation												
16. 1986 M	SJS 1996	1996–2004	OD	1996		1998–2004				6/6	1/60	
			OS	1996–2004						6/6	6/6	
17. 1971 F	TEN 1992	1993–2004	OD	1992†		1993–2004				6/9	HM	
			OS	1992†		1993–2004				6/9	HM	
18. 1978 F	SJS 1996	2001–2004	OD			2001–2004				HM	1/60	Prednisolone
			OS			2001–2004				6/12	6/18	
19. 1951 F	SJS 1959	6/2004– 7/2004	OD			2004				5/60	6/36	
			OS			2004				CF	CF	
20. 1966 M	TEN 2002	2003–2004	OD			2003–2004				HM	HM	
			OS	2003–2004						6/18	6/12	
Patients developing recurrent ocular inflammation (SJS-RI) and/or scleritis (SJS-S) with late surface failure (SJS-OSF)												
21. 1993 F	SJS 1996	1999–2004	OD		1999	2002		2001–2004‡		6/9	6/18	Prednisolone 2002, 2003–2004, Ciclosporin 2003–2004
			OS		1999	2002		2001–2004‡		6/12	HM	Prednisolone 2003 (not tolerated), Azathioprine, Mycophenolate+Ciclosporin
22. 1988 F	SJS 1995	2003–2004	OD			2003–2004		2003–2004 2004	2004	6/9	6/24	Prednisolone, IVMP 2000, 2003
			OS					2003–2004‡ 2004		6/9	CF	Mycophenolate 2001, 2003 Ciclosporin (not tolerated)
23. 1971 F	TEN 1995	1995–2004	OD	1995–2004					2003	6/6	6/6	
			OS	1995		2001–2004			2000	6/12	NPL	
Patients developing early or late ocular mucous membrane pemphigoid (SJS-MMP) with late surface failure												
24. 1933 F	TEN 2002	5/04–9/04	OD			2004	2004 E			2/36	6/24	Prednisolone 2004, Azathioprine 2004, Mycophenolate 2004, Prednisolone+ Cyclophosphamide
			OS	2004			2004 E			6/60	6/18	Prednisolone 2003, Azathioprine 2003, Mycophenolate 2003–2004
25. 1944 F	SJS 2001	2002–2004	OD	2002		2003–2004	2003 E			6/30	CF	Prednisolone 2003, Azathioprine 2003, Mycophenolate 2003–2004
			OS	2002			2003 E			6/15	6/24	Prednisolone, Ciclosporin 2002–2004, Adalimumab 2003–2004; Infliximab+IVMP 2003
26. 1984 F	SJS 2002	2003–2004	OD			2003–2004	2003–2004 E			LP	LP	
			OS			2003–2004	2003–2004 E			LP	LP	
27. 1980 F	TEN 1982	1984–2003	OD	1984		1997–2003	1995–2003 L			6/6	6/18	Dapsone 1997–2000; Sulphapyridine 2002; Prednisolone 2002, 2003
			OS		1984	1997–2003	1995–2003 L			CF	CF	
Patients developing early or late ocular mucous membrane pemphigoid (SJS-MMP)												
28. 1982 M	SJS 1989	1993–2003	OD				2003 L			CF	1/60	Prednisolone+Azathioprine 2004
			OS		1993		2003 L			6/9	6/24	Prednisolone+Mycophenolate 2004

Table 1 Continued												
Case no. DOB Sex	Year of onset	Follow-up dates	Eye	Dates of diagnosis of complications of SJS						VA first	VA last	Systemic immunosuppression
				Mild/ moderate SJS	Severe SJS	Surface failure	SJS-MMP early/late	SJS-RI	SJS-S			
Patients developing recurrent ocular inflammation (SJS-RI) without surface failure												
29. 1934 M	SJS 1939	1977–2004	OD		1977–2004					HM	LP	Prednisolone+Azathioprine 2004
			OS	1977				2002–2004		6/12	6/12	
30. 1961 F	SJS 1987	1995–2004	OD	1995				1996–2004		6/9	6/9	Prednisolone+Mycophenolate
			OS	1995				1996–2004		6/12	6/9	Dapsone 1996–1998 (not tolerated), Azathioprine 1998 (not tolerated)
*Patients who developed severe disease and recovered to moderate disease after treatment (14 OD) or who recovered and later relapsed (15 OD); †eyes with ongoing inflammation (of variable degree), but without progressive scarring; ‡according to data from medical report when discharged from hospital at the resolution of acute episode. CF, count fingers; DOB, year of birth; E, early; F, female; HM, hand movements; L, late; LP, light perception; M, male; OD right eye; OS left eye; SJS, Stevens–Johnson syndrome; SJS-MMP, Stevens–Johnson syndrome-mucous membrane pemphigoid; SJS-RI, Stevens–Johnson syndrome-recurrent inflammation; SJS-S, Stevens–Johnson syndrome-scleritis; TEN, toxic epidermal necrolysis; VA, best corrected visual acuity with patient’s usual correction (unaided, glasses or contact lenses).												

was needed in another three patients to prevent corneal graft rejection (cases 8 and 13) and as complementary treatment of persistent epithelial defect after superficial keratectomy (case 18). Immunosuppressive drugs given included: prednisolone (12 patients), intravenous methylprednisolone (2 patients), dapsone (4 patients), sulphapyridine (1 patient), azathioprine (5 patients), mycophenolate (5 patients), adalimumab (1 patient), ciclosporin (5 patients), infliximab (2 patients) and cyclophosphamide (1 patient).

Apart from two patients, in whom two or more steroid-sparing agents were used simultaneously (cases 26 and 22), the majority were treated with one drug. In some cases, patients required changes in treatment (9 patients), due to either intolerance or inadequate control of inflammation. In one patient (case 30), systemic immunosuppression was not tolerated, so it was discontinued and control of inflammation was achieved with topical corticosteroids. In case 27, dapsone and sulphapyridine were not tolerated, and two recent episodes of inflammation were controlled with short courses of oral prednisolone.

Visual acuity did not change in 16 eyes, increased in 19 eyes and decreased in 21 eyes (table 1).

The individual case reports are given in Appendix 1 available on the BJO website at <http://bjophthalmol.com/supplemental>

DISCUSSION

SJS and TEN are the most severe variants of the spectrum of erythema multiforme, an acute immunological mucocutaneous disorder with high morbidity and mortality, and an incidence of 1.89 per million inhabitants per year.¹³ Approximately 80% of hospitalised patients develop acute ocular complications that are similar for both SJS and TEN, with severe involvement in 25%.^{4–5} The morbidity of the disease may be due to the acute corneal complications, but is more usually due to the results of conjunctival scarring,⁶ with chronic sequelae occurring in approximately 35% of patients.¹⁴

The severity of the consequences of conjunctival scarring range from mild to severe. Some patients in this series presented with mild ocular involvement, caused by mild dry eye or meibomian gland disease, and showed no progression towards the more severe stages. Others presented with severe complications early after the acute stage. However, it is our experience, and that of other authors,^{6–9} that chronic ocular complications after SJS/TEN can present with a variable course that is not always the direct consequence of conjunctival scarring.

Late surface failure (SJS-OSF) may occur in SJS/TEN both without late onset inflammatory disease and also as a consequence of three types of late inflammatory disease: SJS-RI, SJS-S and progressive conjunctival scarring (SJS-MMP).

Surface failure (SJS-OSF) can appear early, as a consequence of severe inflammation in the acute stage of SJS, or can manifest as late as 4 years after the initial onset of the disease.⁷ Destruction of the limbus during the acute phase of the disease may cause stem cell deficiency, but leave enough transient amplifying cells to maintain a normal corneal epithelium for some time after the disease onset; this could explain the evolution from peripheral, or localised, surface failure to complete surface failure within 2 years, which developed in five cases (eight eyes) in this series. Similar findings have been described in one case of SJS and in patients with thermal/chemical injury.⁷ Late stem cell failure may also appear as a result of prolonged limbal inflammation, in cases with recurrent SJS, SJS-MMP and SJS-S, as occurred in eight patients (10 eyes) in this report. For this reason, we strongly recommend aggressive management of any inflammatory episodes.

SJS-RI has been reported in a small group of SJS patients with recurrent conjunctival inflammation unrelated to mechanical irritation or to dryness, but perhaps linked to immune complex vasculitis, and not associated with cutaneous relapses.⁸ In all these patients, the epithelial basement membrane was negative for immunoreactant deposition. The occurrence of scleritis in one patient with SJS has been

Figure 2 Right eye of case 22 showing scleritis (SJS-S).

Figure 3 Right eye of case 27 showing progressive conjunctival cicatrization (SJS-MMP).

reported.¹⁰ SJS-MMP has been described in five cases following an acute episode of severe ocular inflammation after SJS.⁹ The time lag between the onset of SJS and MMP ranged from a few months to 31 years. All five patients had linear immune deposits characteristic of cicatricial pemphigoid along the basement membrane zone of a mucosal biopsy; all responded to systemic immunosuppressive therapy.

We present four cases (seven eyes) of SJS-RI and five cases (10 eyes) of SJS -MMP. Only one (case 27) of the two patients with

SJS-MMP who underwent conjunctival biopsy had immunoglobulin deposition along the basement membrane. However, positive direct immunofluorescence is present in only 50% of patients with ocular MMP,¹⁵ so that this investigation is only helpful when positive.¹⁶ For this reason, four patients were diagnosed as SJS-MMP, following the development of progressive conjunctival scarring, but in the absence of positive immunofluorescence. Progressive cicatricial changes were absent both in our patients with SJS-RI and in the previously described cases.⁸ Conjunctival biopsies in two of our cases of SJS-RI (22, 30) did not show perivascularitis.⁸ SJS-S occurred in two patients (four eyes) and was severe, with limbitis leading to stem cell deficiency in one eye. Robin *et al*¹⁰ have described histopathological findings in a conjunctival-scleral biopsy, similar to those which Foster reported in the conjunctiva of SJS-RI patients⁸; the development of bilateral necrotising sclerokeratitis, after conjunctival inflammation (case 22), could point to a common pathophysiological pathway for both patterns of chronic ocular disease.

As many of these patients were tertiary referrals, we cannot make any statement about the incidence of these different conditions. However, the handful of previous reports suggest these are very infrequent.⁷⁻¹⁰

The management of the chronic stage of SJS/TEN is one of the most challenging problems for the ophthalmologist. Treatment is directed at the management of the ocular surface, eliminating or minimising treatment toxicity and suppressing inflammation.⁶ Successful management requires identification of these different components of the disease, which are not present in all cases. Conjunctival inflammation in SJS may have a non-specific component related to external factors such as trichiasis or severe dry eye²⁴ so that endogenous inflammation cannot be assessed until the external triggering factors of conjunctival inflammation have been controlled; the residual inflammation then reflects the activity of endogenous inflammation in those cases with recurrent or persistent inflammation. It is in these cases that the use of systemic immunosuppression with corticosteroids and/or steroid-sparing agents must be considered; topical corticosteroids are rarely useful in the long term for these cases.⁸⁻¹⁰ Treatment guidelines are similar to those for autoimmune bullous disorders except that the use of sulphonamides should be avoided, as these can precipitate recurrences of SJS.⁶ ¹⁵ If patients have conjunctival inflammation or evidence of progressive conjunctival shrinkage, cataract surgery or oculoplastic surgery on the conjunctiva (as opposed to lid surgery for trichiasis and distichiasis) should be avoided until the disease is controlled by systemic immunosuppressive therapy.¹⁶

This review of patients with SJS/TEN illustrates several different causes of delayed ocular disease (SJS-OSF, SJS-RI, SJS-S and SJS-MMP) that may occur in the natural history of the disease that follows the acute episode of SJS/TEN. These are not recognised by many ophthalmologists because these events have been infrequently reported and are not all described in reviews or in text books. Their recognition is relevant, both to the prognosis for vision and so that appropriate anti-inflammatory therapy can be instituted.

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