Acanthamoeba Sclerokeratitis

Epidemiology, Clinical Features, and Treatment Outcomes

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Purpose: To describe the epidemiology, clinical features, and treatment outcomes of Acanthamoeba sclerokeratitis (ASK).

Design: Retrospective case series.

Participants: All cases of both Acanthamoeba keratitis (AK) and ASK identified between January 1, 2000, and January 8, 2011, at Moorfields Eye Hospital.

Methods: Acanthamoeba keratitis was defined as the presence of AK with concurrent ipsilateral scleral inflammation. Topical steroids and oral nonsteroidal anti-inflammatory drugs (NSAIDs) were used as the first line of treatment. In unresponsive cases, oral NSAIDs were replaced by oral prednisolone with cyclosporine, azathioprine, or mycophenolate as steroid-sparing agents. Cyclosporine was combined with azathioprine or mycophenolate in cases unresponsive to only 1 of these drugs alone.

Main Outcome Measures: Epidemiology, clinical phenotype, response to therapy, resolution of inflammation, visual outcome, corneal transplantation, and enucleation rate.

Results: From a series of 178 patients with AK, 36 eyes of 33 patients (18.5%) developed ASK. A total of 25 of 33 patients (76%) with ASK were tertiary referrals. The incidence of the disease in greater London was 0.13 per million, and the incidence in this population of patients with AK was 33 of 178 (18.5%). Mild scleritis/limbitis responsive to topical steroids and oral NSAIDs was present in 11 of 36 eyes (31%), and moderate/severe scleritis, requiring systemic immunosuppressive therapy, was present in 25 eyes (69%). Before the initiation of ASK treatment, 2 of 36 eyes (6%) had corrected distance visual acuity (CDVA) /20/40. The length of ASK treatment was 15.3/20.7 months. The follow-up after discontinuation of scleritis treatment was 27.2/31.8 months. An improvement in visual acuity was recorded in 23 of 36 eyes (64%). At the final visit, 13 of 36 eyes (36%) had CDVA /20/40. Control of scleral inflammation and pain was achieved in all but 2 eyes (2 enucleations). Cataract developed in 10 of 36 eyes (28%), and 14 of 36 eyes (39%) developed a persistent epithelial defect. Keratoplasty was performed in 21 of 36 eyes (58%), 9 therapeutic/tectonic and 12 for visual rehabilitation. Six eyes had more than 1 keratoplasty. The mild scleritis group had better outcomes in terms of visual improvement and need for keratoplasty.

Conclusions: Acanthamoeba sclerokeratitis is associated with poor clinical outcomes. Management of ASK with anti-inflammatory/immunosuppressive treatment is usually effective in reducing both scleral inflammation and symptoms and possibly reduces the number of enucleations. Ophthalmology 2014;1–8 © 2014 by the American Academy of Ophthalmology.

Acanthamoeba keratitis (AK) is a rare and severe corneal infection primarily affecting contact lens wearers.1 Acanthamoeba is a free-living protozoan that may exist in both a vegetative form (trophozoite) and a dormant form (cyst).2 The cystic form is highly resistant to chemical and physical agents and antibiotic drugs.3 The treatment for this condition requires protracted use of topical antiamoebic medications, mainly biguanides and diamidines.1,4 The main prognostic factor in AK has been identified as the interval between the onset of symptoms and the initiation of the antiamoebic therapy.5,6

Chronic or recurrent corneal inflammation in affected humans is common.7 Necrotic organisms and the walls of amoebic cysts have been shown to elicit an adaptive immune response in an animal model of keratitis8; in humans, they can remain in corneal tissue for years, where they may cause persistent inflammation even when not apparently viable.7 Topical steroids are often used during the course of the disease to control inflammation and reduce tissue destruction.1,4,9

The presence of scleritis, in the context of complications of AK, occurs in approximately 10% of cases, although this may be an underestimation.10–12 The cause of both of the 2 severe inflammatory complications of AK in humans, scleritis1 and severe ischemic posterior segment inflammation,13 is uncertain. These inflammatory complications of AK have not been identified in animal models of the disease. In humans, there is no evidence, for most cases, that the inflammation is accompanied by invasion of the sclera, or posterior segment, by Acanthamoeba. Only 8 cases of
extracorneal invasion of Acanthamoeba complicating AK have been described to date.14–19

The therapeutic approach to Acanthamoeba sclerokeratitis (ASK) has not been standardized. Acanthamoeba sclerokeratitis is associated with a poor prognosis and can lead to enucleation because of uncontrollable pain secondary to inflammation.11,14,20,21 At Moorfields Eye Hospital, we previously proposed a treatment strategy for ASK based on the use of immunosuppressive medications,11 which we justified both because of the poor outcomes of ASK treated with topical steroids and oral nonsteroidal anti-inflammatory drugs (NSAIDs) and because the weight of evidence suggests that ASK is usually a noninfectious response to Acanthamoeba, such that the scleritis and keratitis can be treated independently.

In this study, we reviewed the features and outcomes of previously unreported patients with ASK treated at Moorfields Eye Hospital over the last 12 years.

Methods
All cases of AK treated at Moorfields Eye Hospital between January 1, 2000, and August 1, 2011, were identified by searching the hospital’s electronic database (Epatient) and microbiology database. Patients with ASK were identified from the Epatient database, and their medical records were reviewed. These patients have not been reported in other publications. This study received ethics and institutional committee approval from the Research and Development Department of Moorfields Eye Hospital NHS Foundation Trust. The research adhered to the tenets of the Declaration of Helsinki.

Epidemiology
The postcodes of UK patients and the countries of international patients were recorded and whether their first attendance for this episode of AK was at Moorfields (primary referral) or another hospital from which they were referred for further management (tertiary referral).

Diagnosis
Acanthamoeba keratitis cases were included in the study if they had a positive Acanthamoeba culture or histopathologic confirmation of trophozoites or cysts. Culture-negative cases showing Acanthamoeba cysts on confocal microscopy, together with a typical clinical course and response to treatment, also were included. In the absence of these, patients with perineural corneal infiltrates or a typical clinical course with a response to antiamoebic treatment also were included in the sample.18

Acanthamoeba keratitis was defined as the presence of AK with concurrent ipsilateral scleral inflammation, manifesting as deep pain with globe tenderness associated with engorgement of episcleral and scleral vessels, or the presence of scleral thickening on ultrasonography.

Treatment
The initial treatment of AK at Moorfields Eye Hospital uses topical biguanides (polyhexamethylenebiguanide 0.06% or chlorhexidine 0.2%) as monotherapy or in combination with diamidines (propamidine isethionate 0.1% or hexamidine 0.1%) used hourly day and night for 1 to 2 days, then hourly during the day for 1 week, and then tapered according to clinical severity and signs of ocular surface toxicity. Higher concentrations of polyhexamethylenebiguanide (0.06%) and chlorhexidine (0.2%) were used in recalcitrant cases.

Acanthamoeba sclerokeratitis was treated according to the following step-ladder approach (Fig 1), as described by Lee et al.11 The initial treatment uses oral NSAIDs (flurbiprofen 50–100 mg 3 times daily or diclofenac 50–100 mg twice daily) and topical steroids (dexamethasone 0.1% or prednisolone 0.5%, as required). In severe and unresponsive cases (severe pain that was keeping patients awake at night or complications of scleritis, e.g., hypopyon), oral steroids (prednisolone 1 mg/kg/day) were added to the topical steroid treatment. Unless there was a rapid and full response to oral prednisolone (1 week), then steroid-sparing agents such as cyclosporine (3–7.5 mg/kg/day), mycophenolate (usually 1 g twice per day), or azathioprine (usually 100 mg oral daily) were added to avoid long-term steroid side effects. Intravenous methylprednisolone (1 g/day for 2–3 days) was also used in selected cases to obtain rapid control of severe scleral inflammation. In severe cases, systemic cyclosporine was combined with mycophenolate or azathioprine. A biologic agent (infliximab) has been used in only 1 case of recalcitrant and recurrent ASK at this institution to date. This case is still under treatment and was not included in this series.

Tapering or withdrawal of systemic immunosuppression was based on clinical response. In particularly severe or unresponsive cases of scleritis treated with a combination of systemic immunosuppressants, we administered prophylaxis with oral antifungals (itraconazole 100 mg or voriconazole 200 mg twice daily) to reduce the risk of potential invasion of Acanthamoeba trophozoites into the sclera. Descriptive statistics were used, with data expressed as mean ± standard deviation or median and range.

Results

Epidemiology
A total of 178 patients (190 eyes) with AK were identified, consisting of 80 (44.9%) for whom AK was a primary diagnosis at Moorfields and 83 (46.6%) for whom AK was diagnosed at other hospitals and who were referred to Moorfields for management of unresponsive disease (tertiary referrals). In 15 cases (8.4%), the referral route could not be determined.

Add IV methylprednisolone 1 gram oral daily for 2-3 days in severe cases

Figure 1. Stepladder approach to the treatment of Acanthamoeba sclerokeratitis (ASK). All patients received topical steroids and oral nonsteroidal anti-inflammatory drug (NSAIDs) at the onset of therapy. If these do not control the disease, therapy is stepped up to oral prednisolone. Unless there is rapid control of symptoms with oral prednisolone, then steroid-sparing agents are added, and combination therapy with cyclosporine is used for severe cases. Oral antifungal therapy is used as prophylaxis against scleral invasion by trophozoites in recalcitrant cases treated with a combination of systemic immunosuppressants. IV = intravenous.
Acanthamoeba sclerokeratitis occurred in 33 patients (18.5%), previously unreported (36 eyes), of whom 8 (10.0%) had their primary diagnosis at Moorfields and 25 (30.1%) were tertiary referrals. All but 2 patients with ASK were contact lens wearers. Figure 2 shows the place of residence of these patients according to their National Health Service commissioning area. Twelve of 33 patients were resident in Greater London (population, on average, 7.63 million per year for the study period; available at: http://data.london.gov.uk/datastore/applications/custom-age-tool-ons-mid-year-population-estimates; accessed June 26, 2013), giving an approximate annualized incidence of ASK of 0.13 per million (assuming all patients in Greater London were treated at Moorfields). The remaining patients were referred from the rest of the United Kingdom (n = 16) and overseas (n = 5).

Patient Demographics and Clinical Features, Treatment, and Outcomes

The age range of patients with ASK was 17 to 78 years (median, 38.5 years), of whom 16 were male and 17 were female. Table 1 describes the clinical features and outcomes of patients with ASK. Two different subsets were identified within the whole ASK patient group: 11 of 36 (30.6%) with relatively mild scleritis/limbitis that responded to treatment with topical steroids and oral NSAIDs, and the remaining 25 cases (69.4%) with moderate/severe scleritis that was unresponsive to topical steroid and oral NSAID treatment and required oral immunosuppressive therapy. These 2 subsets are summarized in Table 1 for comparison, both with each other and with the whole patient group. The outcomes of these 2 subsets were different. The time to antiamoebic treatment or development of
scleritis was equivalent in both groups. The length of the scleritis treatment was shorter in the limbitis group, with a higher percentage of eyes with final visual improvement and a lower chance of needing a keratoplasty. All the eyes that underwent multiple keratoplasties were in the moderate/severe scleritis group. Typical cases of mild scleritis/limbitis are shown in Figure 3, and typical cases of moderate/severe scleritis are shown in Figure 4.

The follow-up after discontinuation of the scleritis treatment was 27.2 ± 31.8 months (median, 13.5 months; range, 1–156 months). Recurrent scleral inflammation that required more than 1 cycle of treatment occurred in 5 of 36 eyes (13.9%). Ten eyes developed a cataract during the course of the disease, and 14 eyes developed a persistent epithelial defect, which was treated with an amniotic membrane inlay/onlay or a botulinum toxin–induced ptosis. Recurrence of culture-positive AK after keratoplasty occurred in 2 of 21 cases; 3 therapeutic keratoplasties were required in each of these 2 cases.

There were no local or systemic complications in the cases treated with oral immunosuppressive therapy. An incidental finding of uveal melanoma was reported in 1 of the enucleated eyes.

Posterior scleral thickening on B-scan ultrasonography was reported in 1 of the cases (included in the moderate/severe scleritis group) and eventually resolved with treatment. There was a single case of nodular scleritis in our series; the nodule was biopsied and degenerate cysts were identified using immunohistochemistry, but culture of the biopsy was negative. Intravenous pentamidine, as reported by Kuennen et al,20 was used as an adjunctive antiamoebic treatment. An incidental finding of uveal inflammation that required more than 1 cycle of treatment occurred in 5 of 36 eyes (13.9%). Ten eyes developed a cataract during the course of the disease, and 14 eyes developed a persistent epithelial defect, which was treated with an amniotic membrane inlay/onlay or a botulinum toxin–induced ptosis. Recurrence of culture-positive AK after keratoplasty occurred in 2 of 21 cases; 3 therapeutic keratoplasties were required in each of these 2 cases.

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Discussion

In this case series, we report the clinical features and outcomes of 36 eyes with ASK treated in the past 12 years. This represents the largest series of patients with ASK reported to date and does not include the 19 patients in our previous report.11 The clinical features of patients with ASK in our study were substantially similar to those in the earlier series. Acanthamoeba sclerokeratitis is commonly anterior. Only 1 patient with posterior scleral thickening was observed in both studies. This current study, unlike the previous case series that focused on those patients requiring systemic immunosuppressive therapy, includes patients with less severe scleritis (mild anterior scleritis/limbitis) who did not receive oral immunosuppressive drugs but who responded to more conventional treatment with topical steroids and oral NSAIDs.

Epidemiology

We have been told anecdotally that ASK seems more common in the United Kingdom, with the implication that there is something about our cases or treatment that is different from elsewhere. There are 2 possible reasons for this observation, both of which may apply. The difference in incidence and severity of ASK in different geographic areas could be

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**Table 1. Clinical Features and Outcomes of Patients with Acanthamoeba sclerokeratitis**

<table>
<thead>
<tr>
<th>Clinical Features and Outcomes</th>
<th>All ASK Cases (n = 36 Eyes)</th>
<th>Mild Scleritis/Limbitis ASK Subset (n = 11 eyes)</th>
<th>Moderate/Severe Scleritis ASK Subset (n = 25 eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to diagnosis from onset of symptoms (mo)</td>
<td>1.6±1.6 (0.25–6)</td>
<td>1.4±1.0 (0.3–3)</td>
<td>1.6±1.8 (0.25–6)</td>
</tr>
<tr>
<td>Scleritis at presentation</td>
<td>20 (55)</td>
<td>9 (82)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Time to onset of ASK from onset of symptoms (mo)</td>
<td>3.2±2.7 (0.25–9)</td>
<td>2.8±2.5 (0.3–7)</td>
<td>3.5±2.9 (0.25–9)</td>
</tr>
<tr>
<td>Length of ASK treatment (mo)</td>
<td>15.3±20.7 (8.5–23)</td>
<td>6.2±6.0 (2–23)</td>
<td>19.6±23.8 (9–23)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical steroids</td>
<td>11 (100)</td>
<td>25 (100)</td>
<td></td>
</tr>
<tr>
<td>Oral NSAIDs</td>
<td>11 (100)</td>
<td>25 (100)</td>
<td></td>
</tr>
<tr>
<td>Oral steroids</td>
<td>0</td>
<td>19 (76)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>18 (72)</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>0</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>Oral antifungals</td>
<td>0</td>
<td>8 (32)</td>
<td></td>
</tr>
<tr>
<td>Combination therapy</td>
<td>0</td>
<td>7 (28)</td>
<td></td>
</tr>
<tr>
<td>CDVA ≥20/40 at baseline</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>CDVA ≥20/40 at final visit</td>
<td>13 (36)</td>
<td>6 (54)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>CDVA improved</td>
<td>23 (64)</td>
<td>9 (82)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Scleritis resolved</td>
<td>34 (94)</td>
<td>11 (100)</td>
<td>23 (92)</td>
</tr>
<tr>
<td>Recurrent scleritis</td>
<td>5 (14)</td>
<td>0 (0)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Cataract</td>
<td>10 (28)</td>
<td>2 (18)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Persistent epithelial defect</td>
<td>14 (39)</td>
<td>2 (18)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Keratoplasty</td>
<td>21 (58)</td>
<td>3 (27)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>&gt;1 Keratoplasty</td>
<td>6 (29)</td>
<td>0 (0)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Total no. of keratoplasties</td>
<td>30 (22 PK, 8 LK)</td>
<td>3 (2 PK, 1 LK)</td>
<td>27 (20 PK, 7 LK)</td>
</tr>
<tr>
<td>Reason for keratoplasty</td>
<td>14 T, 16 V</td>
<td>3 V</td>
<td>14 T, 13 V</td>
</tr>
<tr>
<td>Recurrence after keratoplasty</td>
<td>2 (6)</td>
<td>1 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Phthisis</td>
<td>3 (8)</td>
<td>0 (0)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Enucleation</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

ASK = Acanthamoeba sclerokeratitis; CDVA = corrected distance visual acuity; LK = lamellar keratoplasty; PK = penetrating keratoplasty; T = therapeutic/tectonic; V = visual.

Data for each of these 3 datasets are expressed as mean ± standard deviation/median (range) or number (percentage).
secondary to the local prevalence of different *Acanthamoeba* genotypes that are more pathogenic. Alternatively, this number of cases may be due to Moorfields as a tertiary referral center. The incidence of AK is higher in the United Kingdom than elsewhere, and this, coupled with the fact that the Moorfields local catchment for severe disease is approximately 8 million and that for tertiary referrals includes the whole of the United Kingdom (63.7 million as a mid-2012

**Figure 3.** Patients with *Acanthamoeba* keratitis and mild scleritis before the treatment (A, C) and at the last follow-up appointment (B, D).

**Figure 4.** Patients with *Acanthamoeba* keratitis and moderate/severe scleritis before treatment (A, C) and at the last follow-up appointment (B, D).
Pathogenesis

The pathogenesis of ASK remains unclear. It has not been established for certain whether the scleritis results from direct invasion of the sclera by Acanthamoeba trophozoites or whether it is solely an inflammatory process. However, only 8 cases of extracorneal invasion of Acanthamoeba have been described to date.14–19 Five patients with predisposing conditions (meningoencephalitis, immune deficiency, penetrating keratoplasties) developed Acanthamoeba endophthalmitis with Acanthamoeba in the aqueous, vitreous, and retina,15–17 whereas in the remaining 3 cases culture-proven scleral/ intraocular invasion was reported without predisposing factors.14,18,19 In our series, histology of a scleral nodule biopsy showed the presence of degenerated and necrotic cysts, but culture of the scleral scraping from the nodule was negative. Acanthamoeba trophozoites have an exquisite capacity to produce extracellular matrix lysis and tissue destruction though the production of proteases.2,23 Nonetheless, intraocular invasion has been shown to be promptly hampered by the massive engagement of innate immune cells (neutrophils and macrophages) in animal models.24 In vitro and animal studies have demonstrated that trophozoites possess the ability to penetrate through Descemet’s membrane and kill endothelial cells but are cleared from the anterior chamber by a robust neutrophilic reaction.25 The combined results of 2 histologic series did not identify extracorneal invasion of living organisms in a total of 16 eyes enucleated for AK.13,26 Granulomatous inflammation and T lymphocytes invasion of the sclera in the absence of Acanthamoeba cysts or trophozoites was recently described in a case of ASK.27 Also, in vitro studies have proven that necrotic amoeba and cyst remnants can induce an inflammatory response, paralleling the finding of inflammation in human AK eyes associated with nonviable cysts.7 All the patients included in our series were immunocompetent at the time of the onset of scleritis. In our opinion, the scleral inflammation in immunocompetent patients with ASK is usually an inflammatory process in which Acanthamoeba-driven antigen mimicry or a T-cell-mediated vasculitic response (similar to that observed in the ischemic posterior inflammation reported by Awwad et al13) could be the underlying cause of scleral inflammation. However, in light of the few reported cases of scleral invasion and because of the potential for the active Acanthamoeba trophozoite to spread into the sclera as a result of the introduction of immunosuppressive therapy, we used prophylaxis with oral itraconazole or voriconazole in recently treated cases and recommend this for all cases.28–31

Clinical Phenotypes

The eyes included in our study were in 2 groups: those with mild anterior scleritis/limbitis responding to topical steroids and oral NSAIDs, and those with a more severe anterior or posterior scleritis responding only to oral immunosuppressive agents. There was no difference in the time between the onset of symptoms and the initiation of antiamoebic treatment in these 2 groups. Therefore, a delay in antiamoebic treatment did not seem to be a factor in determining the severity of the scleritis. The outcomes of the patients with milder disease responsive to topical steroids and oral NSAIDs were more favorable, none of whom required a therapeutic keratoplasty. Our recent study analyzing the outcomes of patients given topical steroids before the diagnosis of AK, usually following misdiagnosis as herpes simplex keratitis, showed that scleritis was more common in the group treated with steroids before diagnosis.32

Treatment Algorithm

We proposed in a previous study a treatment approach to ASK that is based on immunosuppressive medications.11 Although not widely accepted, control of inflammatory activity by topical steroids is frequently necessary in cases of AK.1 In a recent American survey, the majority of respondents reported the use of topical steroids in AK in at least some cases.4 All anti-inflammatory and immunosuppressive treatments should be administered only in conjunction with antiamoebic medications and discontinued before the suspension of the antiamoebic treatment.

There were 2 cases of recurrent AK after penetrating keratoplasty in patients receiving immunosuppressive treatment. However, this is common in patients receiving therapeutic keratoplasty for AK and steroids and immunosuppressive drugs, when given in association with antiamoebic medications, and did not appear to result in enhanced pathogenicity of the amoeba or relapsing infection.28 Although no systemic side effects were observed in this series, steroids and immunosuppressive medications can cause severe and life-threatening side effects and have to be administered using the appropriate toxicity screening protocols.

Outcomes of Therapy

The high rate of inflammation control and the small number of enucleations in this series suggest this treatment is beneficial in patients for whom severe pain would otherwise result in an enucleation for symptomatic control. Compared with our previous report, outcomes for the patients requiring systemic therapy were similar.11 The immunosuppressive treatment was conducted for a substantially longer time in our most recent series (19.6±23.8 vs. 7.2±3.9 months). Nine of 25 eyes (36%) with severe scleritis underwent therapeutic/tectonic keratoplasty, compared with 10 of 20 eyes (50%) in the previous study. This reduction in the number of emergency keratoplasties was achieved despite similar clinical outcomes (2/25 vs. 2/20 enucleations) and improvement in corrected distance visual acuity. It is

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estimate; http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Population) and some overseas patients, Moorfields probably concentrates more on patients with rare conditions than most major eye hospitals worldwide. These patients often have all their treatment at Moorfields because of the excellent transport links to its central London location. Additional patients are referred as a result of the reciprocal arrangements for health care within the European Union and special arrangements with some other overseas governments, such as Malta.

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possible that the longer period of immunosuppressive treatment may have been beneficial in the recent series.

**Study Limitations**

Treating ASK that is unresponsive to topical steroids or oral NSAIDs with immunosuppressive medications has been the standard of care at Moorfields Eye Hospital for 20 years. Before this, severe pain and morbidity led to enucleation to control the pain, and this still happens, as in this series and other reports of this condition, when the immunologic response to the infection is inadequate. Conducting a formal randomized study would probably require patients with ASK to be randomized to topical steroid or an oral NSAID or an oral immunosuppressant, with patients in either group being taken out of the study and treated with adequate oral immunosuppression when unresponsive to the study medications. Although this study design would bring more rigor to the criteria for therapy, and for the assessment of outcomes, than our current and pragmatic escalating stepladder therapy used for this clinical case series, we think the disease is too rare for such a study to be viable in terms of the numbers required to achieve statistical power for any relevant outcome.

In conclusion, the development of scleritis in patients with AK (33/178 in this series) is associated with high morbidity. A high percentage of patients with ASK require a keratoplasty at some stage. Anti-inflammatory/immunosuppressive treatment improves the symptoms and reduces the scleral inflammation and is likely to reduce the number of enucleations. The corneal and scleral disease in ASK, although interdependent, may require this combined therapeutic approach with concomitant topical and systemic therapy for keratitis together with topical and systemic anti-inflammatory therapy for the scleritis.

**References**

Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AK = Acanthamoeba keratitis; ASK = Acanthamoeba sclerokeratitis; NSAID = nonsteroidal anti-inflammatory drug.

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