AMERICAN ACADEMY™
OF OPHTHALMOLOGY

The Impact of Topical Corticosteroids Used in Conjunction with Antiamoebic Therapy on the Outcome of *Acanthamoeba* Keratitis

Nicole Carnt, PhD, B.Optom,[1,2] *Dana Robaei, PhD, FRANZCO,*[1,2] *Stephanie L. Watson, PhD, FRANZCO,*[2] *Darwin C. Minassian, FRCOphth, MSc(Epidem),*[3] *John K.G. Dart, DM, FRCOphth*[4]

Purpose: To examine the impact of topical corticosteroid use after the start of antiamoebic therapy (AAT) on the outcomes of *Acanthamoeba* keratitis (AK) therapy.

Design: Cohort study.

Participants: A total of 196 patients diagnosed with AK at Moorfields Eye Hospital, London, between January 1991 and April 2012. In 13 patients with bilateral AK, 1 eye was randomly excluded from analysis.

Methods: Patient demographics and clinical examination findings were collected both at the start of AAT and subsequently at the time that topical corticosteroid therapy was initiated. Preliminary a priori investigations were used to identify effect modifiers/confounders and extreme associations requiring consideration in multivariate regression modeling. A multivariable logistic model, optimized for assessment of corticosteroid use after the start of AAT, was used to estimate the odds ratios (ORs) of a suboptimal outcome.

Main Outcome Measures: Suboptimal outcome was defined as final visual acuity $\leq$20/80, corneal perforation, or the need for keratoplasty.

Results: In multivariable analysis, restricted to 129 eyes (1 eye per patient) free of scleritis and hypopyon at the start of AAT, topical corticosteroids were not associated with worse outcomes (OR, 1.08; 95% confidence interval [CI], 0.39−3.03), even when corticosteroids had been used before the start of AAT. Risk factors significantly associated with worse outcomes were topical corticosteroid use before the start of AAT (OR, 3.85; 95% CI, 1.35−11.03), a corneal ring infiltrate (together with at least 1 other feature of AK) present at the start of AAT (OR, 5.89; 95% CI, 1.17−29.67), and age $\geq$33 years at the start of AAT (OR, 4.02; 95% CI, 1.46−11.06).

Conclusions: Many corneal specialists currently are uncertain about the risk benefit associated with the use of topical corticosteroids for the management of inflammatory complications of AK. The evidence from this study gives clinicians and patients reassurance that the potential benefits of topical corticosteroid therapy, for treating pain and discomfort, are not associated with worse outcomes when initiated after starting modern AAT. Other potential benefits, in terms of resolution of inflammatory complications, will not be demonstrated without a carefully designed randomized clinical trial. *Ophthalmology 2016;■:1−7 © 2016 by the American Academy of Ophthalmology.*

Acanthamoeba keratitis (AK) often is associated with severe corneal inflammation and considerable pain.[1] Topical corticosteroids often are prescribed for AK after a period of antiamoebic therapy (AAT) for eyes with persistent inflammation evidenced by scleritis, an anterior chamber reaction, ring infiltrates, and chorioretinitis, all of which are usually associated with pain[1−3] and can result in permanent loss of vision. Topical corticosteroids may improve the quality of life of patients by relieving pain, improving short- and long-term vision, and minimizing the need for enucleation for pain relief.[4]

Clinicians are concerned that topical corticosteroids potentiate infection by downregulating the immune response, which may in turn lead to poorer outcomes. In a recent survey of 82 American corneal specialists, only 9.8% said they used corticosteroids most of the time in the management of AK, with a majority of 52.4% using them some of the time.[5] Overall, 37.8% of these practitioners did not use adjunctive topical corticosteroid therapy for AK management at all, and opinion was divided about the risks and benefits, with 59% believing corticosteroid use was beneficial and 41% believing that their use would result in a poorer outcome.[5] It is clear that the evidence base for the use of topical corticosteroids in the management of AK is inadequate to aid clinical decision-making.

In a cohort of patients treated at Moorfields Eye Hospital NHS Foundation Trust, London, we have recently shown that corticosteroid use before the initiation of AAT is associated with suboptimal outcomes,[6] confirming the findings of small case series from other centers.[4,7,8]

This study was designed to assess the impact of topical corticosteroids on outcomes, when used as part of the

http://dx.doi.org/10.1016/j.ophtha.2016.01.020
ISSN 0161-6420/16

contemporary management of AK in this large patient group at Moorfields Eye Hospital.

Methods

The methods for case ascertainment, the definition of a suboptimal outcome, and the disease staging have been reported,[6] but are summarized in this article.

Case Ascertainment

A retrospective review was conducted of the medical records of patients diagnosed with AK at Moorfields Eye Hospital between January 1991 and April 2012. The Moorfields Eye Hospital Clinical Research Management and Audit Department approved the study, and the Tenets of the Declaration of Helsinki were adhered to.

Cases were included in the analyses if they had a positive *Acanthamoeba* culture or histopathologic confirmation of trophozoites or cysts. Culture-negative cases that were positively identified as having *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.

One eye only of each bilateral case was selected randomly for inclusion in the analysis by sequential reference to a table of random numbers, using the rule right eye if random number is even, otherwise left eye.

Exposure of Primary Interest

Patients were classified into 2 main comparison cohorts according to topical corticosteroid use in the management of AK: those treated with corticosteroids after the start of AAT, who constituted the "exposed" cohort, and those who had not been treated with corticosteroids after the start of AAT, who formed the "unexposed" cohort. Some patients in both groups had been treated with topical steroids before diagnosis and treatment for AK.

Definition of Outcomes

The primary outcome measure was a suboptimal outcome, defined as a final best-available visual acuity $\leq$20/80 (recorded after completion of therapy for the AK episode), corneal perforation, or the need for keratoplasty.[6]

Definition of Disease Staging

Disease stage at presentation was divided into 3 categories[6]: Stage 1 AK was defined as presence of corneal epitheliopathy only. Stage 2 AK was defined by presence of 1 or more of a corneal epithelial defect, perineural infiltrate, or stromal infiltrate, in addition to stage 1 findings. Stage 3 disease required the presence of a corneal ring infiltrate, as well as 1 or more features of stage 2 disease.

Statistical Analyses

Statistical analyses were performed using the STATA software, version 8 (StataCorp LP, College Station, TX). Analysis of the impact of corticosteroid use on final outcomes was restricted to those with available temporal corticosteroid use data and final outcomes.

In estimating the effect of corticosteroid exposure on outcomes, adjustment had to be made for disease severity at the start of AAT to minimize its confounding effect. This was agreed a priori. Scleritis was an important measure of disease severity, as was hypopyon. However, stratification of the data, to remove confounding by scleritis and hypopyon present at the start of AAT, was not possible because of the extreme correlation between exposure to corticosteroids and the presence of scleritis or hypopyon at the start of AAT. This extreme association made it necessary to restrict the multivariable logistic regression to patients free of scleritis and hypopyon at the start of AAT.

To determine the effect of possible bias due to missing data, the characteristics of excluded cases were compared with those included in the multivariable analysis. The frequency of demographic and clinical factors in the 2 exposure groups of primary interest (exposed and not exposed to topical corticosteroids after the initiation of antiamoebic therapy) was tabulated.

Logistic regression models were used to assess the effect of exposures on a suboptimal outcome. The exposure of main interest was topical corticosteroid use after the initiation of antiamoebic therapy, all others being considered as auxiliary variables including the use of topical steroids before the start of AAT (potential confounders/effect modifiers). Preliminary cross-tabulations examining the interrelations of suboptimal outcomes with exposures helped to identify auxiliary variables that could be effect modifiers or important confounders, and thus candidates for inclusion in the logistic models.

The modeling process was designed to arrive at a final logistic model that estimated the odds ratio (OR) for the exposure of main interest, with optimal control of confounding effects, such as the use of steroids before the start of AAT. Auxiliary variables included in the final model were those suspected or known a priori to be associated with the outcome (e.g., AK disease severity at the start of antiamoebic therapy) and the exposure of main interest. Also included were the auxiliaries identified in the modeling process as important confounders on statistical grounds. Likelihood ratio tests were used to assess effect modification by auxiliary variables. Model performance and validity were assessed through post-fit diagnostics.

Cases treated with steroids before the start of AAT were included in this multivariable model, after the findings of a preliminary analysis of data split into 2 strata: (1) those who did not have steroids before the start of AAT and (2) those who did. The *effect* of topical corticosteroid therapy initiated after AAT on outcome was estimated by the adjusted OR (or its equivalent risk ratio) within each stratum. This estimate of *effect* did not vary sufficiently across the 2 strata to signify modification of the true *effect* by use of steroids before the start of AAT (likelihood ratio test $P = 0.465$ indicating no significant *effect modification* or interaction). In other words, in those treated with topical corticosteroids before the start of AAT, the probability of a suboptimal outcome (after adjustment for confounding by other factors) was significantly higher, but much the same, whether or not steroids were used after the start of AAT. In those not treated with steroids before the start of AAT, the probability of a suboptimal outcome, although lower, was also much the same whether or not steroids were used after the start of AAT. These findings demonstrate the fact that a risk factor is not necessarily an effect modifier, which can be a difficult concept to understand.

In view of these preliminary findings, we could not justify exclusion of those cases given steroids before the start of AAT or the analysis of separate multivariable models for these 2 subgroups (topical corticosteroids before the start of AAT and no topical corticosteroids before the start of AAT). Other main considerations for not excluding topical corticosteroids before the start of AAT were (1) generalization of findings: loss of information about the considerable population of patients who are treated with topical corticosteroids before the start of AAT in real life and for whom no