

How much clinical practice is aligned with the Herpetic Eye Disease Study!

Dear Editor,

Herpetic eye disease study (HEDS), a prospective placebo-controlled clinical trial in the early 1990s, has evaluated the role of steroid and oral acyclovir for treating herpes simplex virus (HSV) stromal keratitis.^[1,2] Topical steroid is known to reduce the persistence or progression of stromal inflammation and helps shorten the duration of the disease. Antivirals prevent reactivation of epithelial disease during steroid treatment and recurrence of stromal keratitis when used as prophylaxis. In HEDS, topical trifluridine eyedrop was used instead of topical acyclovir eye ointment as the latter formulation was not available in the United States. HEDS recommendations are considered to be the gold standard; however, these trials are more than 20 years old with conflicting reports on the use of acyclovir.

We assessed the alignment of practice patterns to HEDS in managing HSV immune-stromal keratitis among a cohort of Indian ophthalmologists. Using an online survey tool, SurveyMonkey®, in March 2019, 10 questions were administered in social media forums. A reminder message was sent 4 weeks after initiating the survey.

A total of 71 responses were collected from 650 Indian ophthalmologists. Of the 71 respondents, 63/71 (88.7%) had cornea and anterior segment-based practice. A little more than half (39/71, 54.9%) of the ophthalmologists considered stromal edema as a disease-defining criterion. All respondents considered recurrence as a guide to treatment. More than three-fourths of the respondents (55/71, 77.5%) considered >2 episodes per year sufficient for commencing prophylaxis. Long-term prophylaxis with oral acyclovir was preferred as follows: 12 months (22/71, 31.0%), or >12 months (7/71, 9.8%). The opinion was divided as to the route of administering acyclovir during acute recurrent stromal keratitis, either topical (27/71, 38.0%) or oral (32/71, 45.1%). Prednisolone acetate 1% was the most preferred topical corticosteroid, with 52/71 (73.2%) respondents using it as their first choice of drug in HSV immune stromal keratitis. Although 42/71 (59.2%) preferred the use of topical corticosteroids for a shorter duration of 4–6 weeks, 27/71 (38.0%) preferred using it for 10–12 weeks. In alignment with HEDS, we noted that ophthalmologists considered recurrence as a risk factor for further stromal disease and preferred topical steroid therapy. Contrary to HEDS, oral acyclovir was used for the management of acute episodes and the duration of oral acyclovir prophylaxis was <12 months.

The key HEDS recommendations relevant to immune stromal keratitis include the role of topical corticosteroids in corneal edema, lack of benefit of therapeutic oral acyclovir added to a regimen of topical corticosteroids and topical antivirals, and reduction of risk of recurrence with oral acyclovir.^[1-3]

In a multicentric study from France (357 self-reported cases; 412 ophthalmologists), 53.5% of participants preferred the local route of antiviral drugs, and 30.6% also preferred to add oral antivirals drugs.^[4] Our survey showed that 38% of respondents preferred topical and 45.1% preferred oral antivirals during an acute episode. While these findings are in contradiction to the HEDS recommendations, it is probably based on evidence of

improved aqueous concentrations of acyclovir following oral administration.

Treatment failure in HEDS was 38% for patients on oral acyclovir (400 mg five times a day) and 49% of people on placebo therapy before completion of a 10-week regimen of tapering topical prednisolone phosphate and trifluridine.^[2] We noted a different practice prevalent among our ophthalmologists; 45.1% preferred oral acyclovir for acute recurrence of HSV stromal keratitis.

The HEDS study reported a higher recurrence in the placebo group than those on prophylactic oral acyclovir 400 mg twice daily for 1 year (28% vs. 14%, $P = 0.004$). In the 6-month observation period after discontinuing prophylactic acyclovir, the rate of recurrence in the treated versus the placebo group was comparable.^[5] The preferred practice of prescribing prophylactic acyclovir was <12 months for 59.2% of ophthalmologists in our survey and this finding was not aligned to HEDS recommendations.

HEDS investigators used 1% prednisolone sodium phosphate to significantly reduce the persistence and duration of the stromal inflammation in HSV stromal keratitis.^[1,6] However, corticosteroids could facilitate viral proliferation, predispose to secondary infections with bacteria or fungi, induce cataracts, and raise intraocular pressure. Hence, the frequency of corticosteroids in HSV stromal disease has to be customized to individual needs; in India, 73.2% ($n = 52$) of the respondents prescribed prednisolone acetate 1% as the preferred drug for 4–12 weeks.

The study has potential limitations as it includes data from practice preferences rather than analysis of actual prescriptions and diagnoses. We did not enquire about the use of other antivirals or factors for recall bias. Our questionnaire was a web-based survey, and therefore, may have missed respondents who do not access these platforms. The overall response rate was low.

In conclusion, there was an agreement with HEDS recommendations for the slow taper of topical corticosteroids. Opinion deferred on the route of initial antiviral treatment, and the duration of oral acyclovir prophylaxis. These findings suggest that while HEDS provides gold standards for managing immune stromal keratitis, availability of alternative antiviral agents, socioeconomic considerations, and personal preferences guide physician preferences and practice patterns.

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Conflicts of interest

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