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Voriconazole for Fungal Keratitis

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Dear Editor

In their recently published trial, Sharma et al¹ found topical voriconazole to be more effective than intrastromal voriconazole when added to topical natamycin in patients with recalcitrant fungal keratitis. This trial shares a similar protocol with several of our recent trials: a therapeutic exploratory trial² (referenced by Sharma et al as “MUTT”), a therapeutic confirmatory trial³ (the first Mycotic Ulcer Treatment Trial or MUTT I), and a third trial for which results are not yet available (MUTT II). Here, we would like to clarify their reference to MUTT, and compare the results of our trials with the similarly designed trial by Sharma et al.

The authors reference MUTT as providing nonsignificant evidence of a “2-line improvement with voriconazole” compared with natamycin. The results in question come from the therapeutic exploratory trial.² This study was conducted in preparation for the larger MUTT I therapeutic confirmatory trial,³ both of which compared topical voriconazole and topical natamycin in the treatment of fungal keratitis. The smaller exploratory trial enrolled 120 patients and actually reported a non-significant, 1-line improvement with voriconazole overall; the referenced nonsignificant, 2-line improvement was found among a subset of study subjects in a secondary analysis.² More important, the larger, 368-patient MUTT I found significant evidence that cases did nearly 2 lines worse with voriconazole compared with natamycin.³

One notable difference between our studies and the study by Sharma et al lies in the analysis of the primary outcome. The authors seem to have analyzed 3-month best spectacle-corrected visual acuity (BSCVA) without correcting for baseline visual acuity. There is nothing wrong with a posttest-only study; in fact, when a covariate is not highly correlated with the outcome, it is prudent not to include the covariate in the design.⁴ Baseline BSCVA, however, is highly correlated with final BSCVA. Inclusion would allow comparison with the previous trials, and help to correct for the worse presentation in the intrastromal injection arm. Also, depth of ulcer at presentation has been shown to correlate with perforation; were the 5 deep corneal ulcers the same 5 ulcers that perforated, because the intrastromal arm had both 4 deep ulcers and 4 perforated ulcers and the topical arm had only 1 deep ulcer and 1 ulcer that perforated?

Although the results reported by Sharma et al are not contradictory to those we reported for MUTT I, we still find them unexpected. Why would topical voriconazole fail in our larger study but make a significant difference in this study? Perhaps this discrepancy is related to the different proportions of *Fusarium* cases seen in north India compared with south India. Much of the difference reported in MUTT I could be attributed to *Fusarium* cases.³ Sharma et al also restricted enrollment to patients who did not improve after 2 weeks of treatment with natamycin, whereas natamycin and voriconazole were both started as primary treatment in our trials. Could there be synergy between natamycin and voriconazole? One previous

study reported in vitro evidence of synergy in the combination of a polyene and a triazole at low median concentrations,⁵ although we have found no evidence of synergy in our studies. A larger study may be necessary to confirm any benefit of topical antifungal treatment over injections, as well as to define more clearly the patients for whom such treatment may be most appropriate.

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