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COMMENTED PAPERS - EDITORS CHOICE

Low-dose valacyclovir for Herpes Zoster Ophthalmicus: clinical Insights from the ZEDS trial

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Herpes zoster ophthalmicus (HZO) is a common and clinically significant disease, affecting approximately 8% of the nearly one million Americans who develop herpes zoster each year. Building on the Herpetic Eye Disease Study Acyclovir Prevention Trial, which demonstrated that one year of suppressive acyclovir markedly reduced recurrent herpes simplex keratitis, cornea specialists worldwide have widely extrapolated this practice to HZO by prescribing long-term valacyclovir despite the lack of robust supporting evidence. The Zoster Eye Disease Study (ZEDS), recently published in JAMA Ophthalmology, was designed to address this gap.

The ZEDS was a methodologically rigorous trial: multicenter (95 sites, including international participation), randomized, double-masked, and placebo-controlled, with full ethical oversight and an independent data and safety monitoring committee. Its primary objective was to determine whether suppressive valacyclovir 1,000mg/day for 12 months could delay new or worsening stromal keratitis, endothelial keratitis, iritis, or dendriform epithelial keratitis. A secondary endpoint at 18 months assessed the persistence of benefit.

The trial faced substantial challenges. Of the initially planned 1,050 participants, only 527 were ultimately randomized, reflecting recruitment difficulties compounded by the COVID-19 pandemic and, paradoxically, by entrenched prescribing practices: many cornea specialists were reluctant to randomize patients to a placebo because they were already convinced of valacyclovir's efficacy. An additional disruption occurred in April 2023, when the FDA recalled certain ingredient lots, requiring the temporary suspension of study medication in 47 participants for approximately 5 weeks.

The primary endpoint was not met: at 12 months, recurrence occurred in 28% of the valacyclovir group compared with 33% of the placebo group (hazard ratio [HR], 0.77; p=0.09). At 18 months, however, recurrence rates were 32% versus 40% (HR, 0.73; p=0.03), reaching statistical significance.

Greater clinical clarity emerged from the subgroup analyses. Among participants with recent-onset disease (<6 months), valacyclovir reduced the risk of recurrence by approximately 35% (HR, 0.65) at 12 and 18 months, whereas no benefit was observed in chronic disease (≥6 months). Age (<60 vs. ≥60 years) did not modify the treatment effect. Equally important, frailty model analysis demonstrated a significant reduction in multiple recurrences in the valacyclovir group at 12 and 18 months (HR, 0.69 and 0.71, respectively; p=0.02 for both), a clinically meaningful finding given that recurrent episodes drive corneal scarring, neurotrophic keratopathy, and vision loss.

Practical implications

Despite its limitations, ZEDS represents the highest-quality evidence currently available on this question and exceeds the methodological standard of most

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published HZO research. The clinical message is nuanced yet actionable: routine suppressive valacyclovir does not appear justified for patients with longstanding HZO (≥6 months after the acute episode), whereas selected patients, particularly those with recent-onset disease or recurrent flare-ups, may derive meaningful benefit. Perhaps the most enduring contribution of ZEDS is the reminder that the most effective intervention against HZO lies upstream: clinicians should strongly advocate recombinant zoster vaccination rather than focus solely on treating its complications.