Lifitegrast in Clinical Practice: What the Evidence Actually Tells Us — and What It Does Not

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Dry eye disease (DED) is among the most common conditions a general ophthalmologist encounters. The waiting room recognises it. The slit lamp confirms it. And yet, when it comes to anti-inflammatory pharmacotherapy, clinical decision-making remains surprisingly uncertain. The arrival of lifitegrast 5% ophthalmic solution, a small molecule LFA-1 antagonist approved by the US FDA in 2016, raised expectations of a cleaner answer. More than eight years on, those expectations deserve an honest appraisal.

This editorial is addressed not to the dry eye sub-specialist, but to the general ophthalmologist who reaches, at some point, for an anti-inflammatory agent in a patient whose lubricants have failed. The question is practical: should that agent be lifitegrast, cyclosporine, and if so, which one, and for whom?

The answer, as we will see, is less straightforward than the prescribing literature suggests. And understanding why is itself clinically useful.

THE MECHANISM, AND WHY IT MATTERS CLINICALLY

Cyclosporine and lifitegrast are both anti-inflammatory. Both target T-cell-mediated ocular surface inflammation. But they work at different points in the inflammatory cascade, and this distinction is not merely academic.[1]

Cyclosporine inhibits calcineurin, blocking the transcription of pro-inflammatory cytokines including IL-2, thereby suppressing T-cell activation upstream. Lifitegrast, by contrast, blocks the interaction between LFA-1 on leukocytes and ICAM-1 on the ocular surface, interrupting T-cell recruitment and adhesion at a later, more downstream step in the cascade.[2]

Cyclosporine acts earlier in the inflammatory pathway. Lifitegrast acts at the point of T-cell recruitment to the ocular surface. This mechanistic difference has real implications for the type of patient who responds to each agent.

In meibomian gland dysfunction (MGD), ICAM-1 expression in the tear film is elevated. The LFA-1/ICAM-1 axis that lifitegrast targets is therefore particularly relevant in the evaporative dry eye phenotype. In contrast, cyclosporine's broader immunosuppressive profile may confer advantage in aqueous-deficient or autoimmune-driven disease, where upstream T-cell suppression is the priority. However, using both does not significantly improve visual acuity or punctate epithelial erosions comparison with controls. Autoimmune disease significantly impacts efficacy of dry eye diseases treatment protocols.[3]

For the general ophthalmologist, this suggests a first practical principle: the mechanism favours lifitegrast in screen-associated, MGD-driven evaporative dry eye, and cyclosporine in aqueous deficiency, and autoimmune disease.

WHAT THE OPUS TRIALS SHOWED, AND THE GAP WE MUST ACKNOWLEDGE

The pivotal programme for lifitegrast comprised four randomised controlled trials: OPUS-1, OPUS-2, OPUS-3, and the open-label SONATA safety study. The results were broadly positive, and lifitegrast demonstrated statistically significant improvements in both symptom and sign endpoints compared with vehicle.[4]

However, the pattern within those results deserves closer attention than it typically receives.

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Symptom improvement, particularly on the Eye Dryness Score (EDS), was consistent and robust across the OPUS programme. Sign improvement, notably in inferior corneal fluorescein staining, reached statistical significance in OPUS-1 and OPUS-2 but showed more modest effect sizes. Objective sign improvements appeared less consistent across studies than symptom outcomes. OPUS-3 met its primary sign endpoint (inferior corneal staining) only at certain time points, and its symptom data were more compelling than its objective findings overall. The impact on eye dryness scores was noted as early as two weeks in OPUS-3 subjects.[4,5]

Lifitegrast relieves how the eye feels, often meaningfully and quickly. Its effect on what the slit lamp shows is real, but more variable. Both matter. Neither should be ignored.

This symptom-sign dissociation is not a flaw unique to lifitegrast. It reflects a fundamental challenge in dry eye trial design: symptoms and signs in DED correlate poorly, even at baseline. Patients with severe staining can be minimally symptomatic. Patients with profound discomfort can have near-normal staining scores. When trials optimise for one domain, the other may lag.

The practical implication is important: if a patient's primary burden is symptomatic, burning, gritty eyes, discomfort on screen use, lifitegrast has strong trial-based support. If the clinical priority is objective surface disease, a longer course and close monitoring are warranted before concluding treatment has failed.

COMPARING LIFITEGRAST WITH CYCLOSPORINE: AN HONEST ASSESSMENT

The most common question in clinical practice is not whether lifitegrast works, but whether it works better or differently than cyclosporine. This is a reasonable question. The honest answer is that the evidence base is insufficient to answer it definitively, not because the question is unanswerable, but because no adequately powered, prospective head-to-head trial has been completed.[6-12]

What we have instead are retrospective comparative data and indirect cross-trial comparisons. A retrospective study found that among 64 patients who had used both agents, more patients preferred cyclosporine (33), than lifitegrast (14), while 12 had no preferences, and 5 could tolerate neither. But critically, no clinical variable predicted who would prefer which agent. Not demographics, not comorbidities, not ocular surface findings.[7]

Remember the other layer of complexity: cyclosporine appeared to confer visual acuity benefit specifically in patients with autoimmune disease comorbidity, with and without lifitegrast a benefit not seen in non-autoimmune DED patients, and not replicated with lifitegrast.[3]

The reason we cannot confidently compare the two drugs is not a gap in clinical experience, it is a gap in trial design. Cyclosporine trials were approved largely on objective endpoints (corneal staining, Schirmer's). Lifitegrast trials gave greater weight to patient-reported symptom endpoints. Comparing them is comparing different questions.

This matters practically. When a patient has already failed cyclosporine, switching to lifitegrast is a rational step, and vice versa. The mechanistic differences described above suggest that patients do not simply fail anti-inflammatory therapy; they may fail one agent at one point in the cascade while remaining responsive to another. Sequencing and switching deserves more deliberate thought than it typically gets in busy clinical practice.

ONSET, TOLERABILITY, AND THE PATIENT CONVERSATION

One underappreciated advantage of lifitegrast is its speed of onset. Symptom improvement in the OPUS trials was observed as early as two weeks, faster than the three-to-six month timeframe typically associated with cyclosporine's therapeutic effect.[4]

This is not a trivial point. Patient adherence to dry eye therapy is notoriously poor, and early symptom relief significantly increases the likelihood of continued use. For the motivated but frustrated patient who has already waited months without benefit from lubricants, early symptomatic improvement from lifitegrast can be the difference between adherence and abandonment.[9]

On tolerability, the picture is more nuanced. Burning on instillation and dysgeusia (an unpleasant taste sensation) are the most frequently reported adverse effects of lifitegrast, occurring in approximately 15–20% of users. Cyclosporine is associated with burning on instillation in roughly 15% of patients. Neither drug is entirely comfortable, but the side effect profiles differ, and individual patient tolerance varies considerably.

For the general ophthalmologist, the practical guidance is this: counsel the patient about both the likely early symptomatic benefit and the possible instillation discomfort before prescribing. The patient who expects one and encounters the other will stop the drug.

A Possible Framework for the General Ophthalmologist

The Cochrane Database Systemic Review results are still awaited.[12] Given the available evidence on record,

a pragmatic clinical framework, not a protocol, may be offered for patient selection in routine practice.

Consider lifitegrast first when: the predominant burden is symptomatic; the dry eye phenotype is evaporative or screen-associated; the patient has previously discontinued cyclosporine due to lack of early effect; or where rapid symptomatic relief is a therapeutic priority.

Consider cyclosporine first when: aqueous deficiency is the dominant mechanism; autoimmune disease is present; objective sign improvement is the primary goal; or cost or availability constraints make lifitegrast inaccessible.

Consider sequencing, and in selected cases combination therapy may be explored where monotherapy has produced partial response; one drug has improved symptoms without signs, or signs without symptoms; or the patient has complex, mixed-mechanism DED.

Neither drug is universally superior. Both are justified first-line agents for inflammatory dry eye. The clinical context, including phenotype, prior treatment, patient priorities, should determine the choice, not habit or convenience.

CONCLUSION

Lifitegrast is a clinically meaningful addition to the dry eye armamentarium. Its mechanism is distinct from cyclosporine. Its symptom data are strong and fast. Its sign data are real but variable. And its direct comparison with cyclosporine remains, for now, an open question, one that an adequately powered head-to-head trial could, and should, one day answer.

Until that trial exists, the general ophthalmologist is best served not by a league table of drugs, but by a clear understanding of what each drug does, for which patients, and what a meaningful response looks like. That understanding is what this editorial has attempted to provide.

Dry eye is a disease of individuals like you and me. It rewards thoughtful prescribing.

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There are no conflicts of interest.

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