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EDITORIAL

Real-world safety data for brimonidine tartrate: is there potential for overuse?

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1. Introduction

Ocular redness is a common ophthalmic complaint, with a number of infectious and noninfectious causes [1]. It arises from dilation of conjunctival blood vessels and, while potentially asymptomatic, it can be associated with reduced quality of life due to discomfort or cosmetic concerns [1].

Treatment of ocular redness should, where possible, be specific to the underlying cause, but temporary relief of nonspecific redness, without significant pathology, can be achieved with topical, over-the-counter ophthalmic vasoconstrictors [2]. Currently available products act as α-adrenergic receptor (AR) agonists to induce constriction of the dilated blood vessels [1,2]; however, chronic use has raised concerns and patients are advised to discontinue use and consult a doctor if redness continues or worsens, or persists beyond 72 h [2]. Here, we present a snapshot of real-world data exploring the potential for overuse of one particular AR agonist: brimonidine tartrate.

2. Brimonidine tartrate

Brimonidine tartrate is a third generation, selective α2-AR agonist, with a relative binding affinity for α2 vs α1 of approximately 1000:1, exhibiting potent vasoconstrictor activity at concentrations as low as 0.025% [1,3,4]. In contrast, other approved topical ophthalmic vasoconstrictors are either α1-AR agonists (such as tetrahydrozoline) or mixed α1/α2-AR agonists (such as naphazoline or oxymetazoline), with α2:α1 binding affinities of around 2:1 or 5:1, respectively [1]. Through its selectivity for α2, brimonidine has greater constrictive effect on conjunctival venules than arteries, as α2-ARs are predominantly expressed in veins [5].

As discussed in Ackerman *et al.* [6], brimonidine tartrate at higher concentrations (0.15% and 0.2%) is approved for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. When used peri-operatively at concentrations from 0.025% to 0.2%, brimonidine is reported to induce conjunctival blanching before ocular surgery, control bleeding during surgery, and prevent bleeding from intravitreal injections. Additionally, brimonidine can reduce pupil size and has demonstrated clinical utilization for patients with a history of refractive surgery who experience night visual problems including glare and halo [7].

Adverse events known to be associated with sustained use of α1-AR agonists include tachyphylaxis (tolerance or loss of effectiveness with continued use) [8,9] and rebound redness (worsening of condition, compared with baseline) [10]; sustained use of α1/α2-AR agonists is also associated with rhinitis medicamentosa [10]. The specific action of brimonidine on α2-ARs is hypothesized to reduce the potential for these adverse events and contribute to a distinct safety profile [1,3].

Two randomized, vehicle-controlled, Phase 2/3 and Phase 3 efficacy and safety studies in participants bilaterally dosed with four-times-daily brimonidine tartrate 0.025% ophthalmic solution over 4 weeks demonstrated significantly reduced ocular redness for up to 8 h, with no tachyphylaxis during treatment and negligible rebound redness 1 week after treatment discontinuation (1.28%; identified in only one of 78 brimonidine-treated participants by investigator assessment). Side effects observed with other vasoconstrictors, such as hypotension, cardiac arrhythmia, or drowsiness, did not present in brimonidine-treated eyes; ocular adverse events such as allergic reactions were minimal and there were no reports of conjunctivitis [4,6,11]. Participant descriptions of their experience with brimonidine treatment were largely positive [4].

Brimonidine tartrate ophthalmic solution 0.025% (LUMIFY) is the first selective α2-AR agonist approved for treatment of ocular redness and [1], based on the clinical findings, the LUMIFY Drug Facts did not warrant a warning that overuse can lead to increased eye redness [12]. This is in contrast with the labeling for all other topical vasoconstrictors marketed in the U.S.

At a higher dose (0.2%), delayed hypersensitivity to brimonidine, often presenting as follicular conjunctivitis, was observed in patients with high intraocular pressure and extended use of brimonidine [13].

This highlights the need for longer-term data to fully elucidate the risk of possible allergic response and establish complete efficacy and safety profiles. Longer-term and observational data would also provide insight into the potential impact of overuse in a real-world setting. Global pharmacovigilance data for LUMIFY from May 2018 to December 2022, during which 49.9 million units were sold, revealed post-marketing adverse event reports that may be associated with overuse and subsequent increased redness due to tachyphylaxis and/or rebound (dependent on MedDRA coding; Table 1).

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Table 1. Post-marketing, real-world reports of adverse events potentially related to overuse of LUMIFY from May 2018 to December 2022 (49.9 million units sold).

Reported adverse event	Number of events
Ocular hyperemia	341
Drug effect less than expected	6
Drug ineffective	503
Drug tolerance	1
Intentional product misuse	2
Rebound effect	60
Symptom recurrence	9
Therapeutic product effect decreased	71
Therapeutic product effect incomplete	423
Therapeutic product effect shortened	1

While it is important to note that reports of adverse events do not establish causality, and the voluntary nature of self-reporting can result in an underestimation of the true incidence, this post-marketing real-world adverse event profile provides insight into the longer-term safety of LUMIFY, with few reports of tachyphylaxis and rebound redness. When used as directed, this experience is aligned with our collective clinical experience of managing ocular redness with brimonidine tartrate ophthalmic solution 0.025% with hundreds of patients since the approval of LUMIFY in our practice.

3. Conclusion

The potential for abuse and overuse exists with any over-the-counter topical vasoconstrictor, meaning use should be targeted and driven by clear clinical need; however, differences between individual products should be considered. Although no head-to-head studies directly compare current over-the-counter ophthalmic vasoconstrictors, the specificity of brimonidine for α2-AR might reduce off-target drug effects and may confer a reduced risk of tachyphylaxis and rebound redness, with currently available clinical data indicating a distinct safety profile that is reflected in the absence of warning in the LUMIFY label [4,6,11]. The specific action of brimonidine, together with clinical study findings and reassuring post-marketing safety data, suggest the risk of adverse impact, when used as directed, is lower for brimonidine than with other available products.

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Declaration of interest

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Reviewer disclosure

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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