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Iontophoretic Delivery of Dexamethasone Phosphate for Non-infectious, Non-necrotizing Anterior Scleritis, Dose-Finding Clinical Trial

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Summary

Currently available treatment options for non-infectious scleritis, including NSAIDs, systemic corticosteroids and immunosuppressive therapies, have both efficacy and side effect limitations.

Iontophoretic delivery of corticosteroids has been demonstrated to be effective for anterior uveitis

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Contributorship statement

Conception and design of study: John Kempen

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and represents a potential new approach to scleritis therapy. We hypothesized that iontophoretic delivery would provide effective and precise medication delivery to the sclera, while limiting systemic exposure and side effects. This first in human randomized, double-masked, dose-escalating study of iontophoretic administration of dexamethasone phosphate for scleritis suggests the treatment to be well-tolerated and safe (within the limitations of the 18 patient sample size). There was a suggestion of efficacy in the lowest (1.2 mA-min at 0.4 mA) dose group (corresponding to the superficial location of scleritis compared to anterior uveitis), with 5/7 eyes meeting the primary efficacy outcome within 28 days. Our results suggest iontophoretic delivery of corticosteroids is a promising potential treatment for scleritis, with favorable safety and preliminary efficacy results in this phase 1 trial.

Management of non-infectious, non-necrotizing scleritis traditionally uses systemic therapy (non-steroidal anti-inflammatory drugs, progressing to systemic corticosteroids, then immunosuppressive therapy for corticosteroid-dependent or refractory cases).¹ These treatments sometimes have systemic side effects, incomplete efficacy, and/or slow onset of action. Subconjunctival corticosteroid injection treatment has had exceptional results—complete suppression of scleritis within 6 weeks in 36 of 38 cases²—but carries a risk of cataract formation, increased intraocular pressure, and possibly scleral melt.²

A potential new approach is iontophoretic delivery of corticosteroid—using electropulsion to push charged medication into the eye, which was well-tolerated and effective in the treatment of non-infectious anterior uveitis³, suggesting that it also may be effective in treatment of anterior scleritis.

As a first-in-human assessment of this concept, we conducted a randomized, double-masked, dose-escalating study of iontophoretic delivery of EGP-437 (anionic dexamethasone phosphate ophthalmic solution 40 mg/mL) in 18 subjects (20 eyes) with mild to moderate non-infectious, non-necrotizing anterior scleritis. We used the Eyegate Pharmaceuticals, Inc. (Waltham, MA) applicator; its inert electrode stimulates electrolysis of water, producing ions to repel drug molecules into the eye.³ Three doses of electric field applied to the same amount of dexamethasone phosphate on the applicator, each given over three minutes, were selected based on results of preclinical and clinical trial (anterior uveitis and dry eye) studies: (1) 1.2 mA-min at 0.4 mA (“lowest” dose), (2) 2.5 mA-min at 0.8 mA (“middle” dose), and (3) 4.5 mA-min at 1.5 mA (“highest” dose). In our dose-escalation design, each group of six patients enrolled were followed for 56 days and a safety assessment was completed before enrollment began for the next higher dose level.

Following active iontophoretic treatment on the day of enrollment (Day 0) for all eyes with scleritis, subjects within each dose group were randomized 1:1 to receive, on day 7, either a second same-dose treatment of EGP-437 (active/active arm) or sodium citrate buffer solution 100 mM at the same iontophoresis setting (active/sham arm). Follow-up visits on days 8, 14, 28, and 56 assessed outcome. Vital signs, visual acuity, ocular pain, external ophthalmologic exam, biomicroscopy, tonometry, corneal fluorescein staining, dilated fundus exam, concomitant medications, and adverse events were followed regularly through day 56.

Tolerability parameters assessed were treatment-emergent ocular symptoms or treatment discontinuation due to side effects. Safety parameters assessed were adverse events, treatment-emergent abnormal examination findings, visual acuity, intraocular pressure, and laboratory results. The primary efficacy parameter was improvement on the Scleritis Severity Score (range 0–20) by at least four steps or to score=0.⁴

The trial, conducted in accordance with the principles of the Declaration of Helsinki, was approved by the Institutional Review Boards of the five participating centers, and was performed in compliance with all applicable laws. It is registered on clinicaltrials.gov (NCT01059955) and was conducted under a Food and Drug Administration Investigational New Drug Exemption. Informed consent was obtained for all subjects.

We enrolled 18 subjects at five sites, treating 20 eyes with active scleritis (with bilateral treatment for bilateral disease). The average age was 49.5 years; 61% of subjects were male. The baseline scleritis severity score range, 1–8, reflects mild to moderate severity (Table 1).

Because no instances of dose-limiting toxicity occurred at any dose level, all doses met criteria for tolerability. The most common adverse events reported were symptoms of active scleritis: ocular or periorbital pain (n= 7), exacerbation of scleritis (n= 8), and headache (n= 4). One eye in the low-dose active/active arm had 2.4 lines' worsening in visual acuity; two eyes had 2–3 lines improvement from baseline (in the low dose sham arm at 14+ days and the mid-dose sham arm at 28 days). The remaining 17 eyes remained within 2 lines of baseline visual acuity throughout follow-up. Average, IOP decreased slightly during follow-up; two eyes had temporary increase of IOP by 6 mmHg from baseline (peak IOP=23 and 22 mmHg in the 1.2 and 4.5 mA-min groups at 7 days after the first treatment), each subsequently improving.

In the lowest dose group, after one treatment 4/7 eyes met the primary efficacy outcome by seven days (before the second (active/sham) treatment; see Table). The remaining eye in the active/active arm achieved the primary outcome subsequently. Two initially responsive eyes subsequently developed rebound scleritis activity after completing treatment. For the other eyes—both in the active/sham arm—one had little change, and one was rescued due to worsening. In the middle dose group, none by 7 days, one (an active/sham eye) by 14 days, and two by 28 days (one each in the active/active and active/sham arms) met the primary outcome. Two other eyes (active/active arm) were rescued due to worsening scleritis, and the remaining two eyes (active/sham arm) neither improved markedly, nor worsened to a point that required rescue. In the highest dose group, two of six met the primary outcome within a week. One eye in the active/active arm required rescue due to failure to resolve by 14 days, and the others did not markedly change status. See supplementary file for longitudinal individual Scleritis Severity Scores.

In summary, this phase 1 first-in-human study of iontophoretic delivery of dexamethasone phosphate for mild to moderate, non-infectious, non-necrotizing anterior scleritis in humans suggested the treatment is well tolerated. The preliminary efficacy signal suggests it is potentially useful as a treatment for scleritis. A lower electrical field dose than used for uveitis (1.2 mA-min at 0.4 mA) appears the most promising among those studied, perhaps

because the site of inflammation is more superficial than in anterior uveitis. Perhaps the higher doses the electric field drove the medication too deep, past the level of inflammation. Given potentially greater safety of iontophoretic delivery of dexamethasone phosphate vis-à-vis systemic and subconjunctival corticosteroid use, further study should be performed to further clarify the utility of this treatment. Dosing frequency in our study was limited based on safety data at the time the study began; future studies could evaluate more frequent dosing schedules, perhaps administering treatments until quiescence is achieved, followed by a treat and extend approach to maintain control thereafter.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Outcome of Patients with Active Non-infectious Scleritis Receiving Dexamethasone Phosphate via Iontophoretic Delivery

Table 1

Eyes (N)	7	7	6
Average baseline scleritis severity score (range)	4.86 (2, 8)	4.0 (1, 7)	3.5 (1, 4)
Days 1 to 7			
Dose-limiting toxicity	0	0	0
Rescue therapy instituted*	0	0	0
Primary efficacy outcome: 4-step improvement in scleritis scale from baseline**, n (%)	4 (57)	0 (0)	2 (33)
4-point improvement in ocular pain score from baseline** n(%)	5 (71)	2 (29)	2 (33)
Days 1 to 56			
Second treatment on day 8 (N##), after randomization			
Dose-limiting toxicity	0	0	0
Rescue therapy instituted*	2	2	1
Primary efficacy outcome: 4-step improvement in scleritis scale from baseline, n (%)**	4 (100)	1 (33)	2 (67)
4 point improvement in ocular pain scale score from baseline, n (%)**	4 (100)	2 (67)	3 (100)
Day 56			
Mean change in IOP (range)*** in mmHg	-2.5 (-4,0)	-2 (-4,1)	-1.33 (-8,2)
Mean change in BCVA (range)*** in, letters	-2.5 (-12, 6)	-3 (-4, -2)	-0.33 (-4,1)

IOP=intraocular pressure. BCVA=best-corrected visual acuity.

* after rescue therapy, subsequent outcomes were censored given that they could not be attributed to study vs. rescue treatment.

** or to the floor. The scleritis scale values range from 0–20; the pain score range was 0–10.

Eyes randomized to specified treatment group

*** among all eyes to end of study period or to rescue visit