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Topical fosaprepitant for the treatment of ocular pain and inflammation

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ABSTRACT

Purpose: To assess whether topical administration of fosaprepitant improves intractable chronic ocular pain and inflammation.

Methods: We report three clinical cases of female patients with drug-resistant ocular pain associated with inflammatory diseases of the ocular surface. The patients were treated for 3 (case 1) and 4 (cases 2–3) weeks with fosaprepitant eyedrops (0.1 mg/mL for case 1; 10 mg/mL for case 2–3). Patients were then followed up for at least 3 weeks. We measured ocular pain with the Visual Analogue Scale (VAS), the Ocular Surface Disease Index (OSDI), and corneal sensitivity with the Cochet-Bonnet esthesiometry. Slit-lamp photography and corneal confocal imaging were used to assess ocular surface integrity/conjunctival hyperemia and corneal nerve morphology, respectively.

Results: All three patients had severe ocular pain (score higher than 6/10 VAS scale). All patients reported a significant improvement in ocular pain after 1 week of treatment. We also observed reduced corneal epitheliopathy (case 1) and conjunctival hyperemia (cases 1–2). In two patients (cases 2–3) the treatment was repeated after 1 year and 9 weeks, respectively, and pain reduction was similar in magnitude to what we observed after the first administration.

Conclusions: Topical administration of fosaprepitant ameliorates ocular pain and clinical symptoms in three patients with intractable ocular pain associated with inflammatory diseases of the ocular surface, without adverse effects.

Importance: Fosaprepitant instillation holds promise as a treatment of chronic ocular pain, an area of unmet medical need.

1. Introduction

Ocular pain is one of the most common symptoms of ocular surface disorders.[1,2] Although it is highly prevalent,[1] available treatments are not specific and are associated with severe side effects. Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and systemic analgesics are all potentially associated with severe local (corneal melting, cataract, increased intraocular pressure (IOP), delayed wound healing[3,4]) or systemic (renal/gastric toxicity, mental impairment/addiction for systemic NSAIDs or opioids) side effects[5,6], especially with chronic use.

Substance P (SP), a neuropeptide released by corneal nerves, has a key role in promoting ocular surface pain and neuroinflammation.[7,8] The release of Substance P is enhanced after ocular surface injury and promotes corneal perforation and opacity.[7,9] Notably, SP exerts its function preferentially via the neurokinin-1 receptor (NK1R), expressed both on neuronal and non-neuronal corneal cells.[8,9]

We and others previously found that the NK1R antagonists, including fosaprepitant, strongly inhibit corneal pain, inflammation, and neovascularization in multiple pre-clinical models of ocular surface disease[9]–.[11] Moreover, we reported that SP levels are increased in the tear fluid of patients with severe ocular surface inflammation and are related to disease severity.[8] Fosaprepitant is a registered drug for treating chemotherapy-induced nausea and vomiting[12] and can be easily formulated as eye drops.

Here, we report three cases of patients affected by intractable ocular pain who were successfully treated with topical fosaprepitant.

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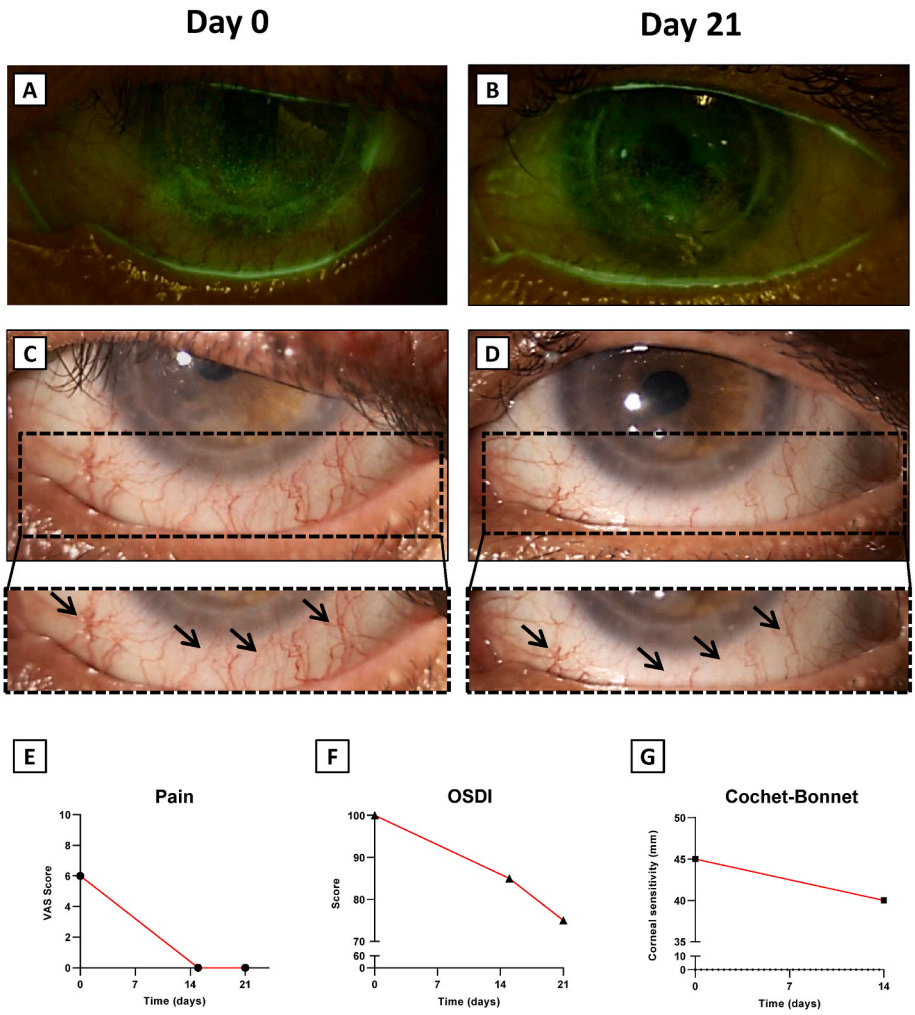

Fig. 1. Clinical outcomes and biomicroscopy result in case #1.
Corneal fluorescein staining demonstrates that topical fosaprepitant is not toxic for the ocular surface and improves punctate keratopathy (A–B). Topical administration of fosaprepitant effectively reduces corneal inflammation and redness after 3 weeks of treatment (C–D). The hatched area and arrows in figures C–D highlight a focus on inflammation and hyperemia in the cornea before (C) and after (D) treatment. The patient reports a reduction in ocular pain (E–F) during treatment, measured by VAS and OSDI questionnaires. Topical instillation of fosaprepitant does not affect corneal sensitivity (G), assessed using Cochet-Bonnet esthensiometer. The data are referred to the left eye.

2. Materials and methods

2.1. Patients and methods

Three patients were referred to the Cornea and Ocular Surface clinic of San Raffaele Hospital, Milan, Italy, for chronic and intractable ocular pain. The hospital's ethics committee approved the compassionate use of the drug.

Fosaprepitant eyedrop was prepared without additional preservatives under sterile conditions using phosphate-buffered saline (PBS) as a vehicle and checking the pH. The patients were treated for 3 (case 1) and 4 (cases 2–3) weeks with fosaprepitant and followed up for at least 3 weeks.

We measured ocular pain with the Visual Analogue Scale (VAS) and the Ocular Surface Disease Index (OSDI); corneal sensitivity with Cochet-Bonnet esthesiometry. Slit-lamp biomicroscopy pictures of the ocular surface (with and without fluorescein staining) were collected before and after treatment. In vivo confocal microscopy was used to image corneal neuropathy in case 3.

2.1.1. Case #1

This was a 71-year-old woman affected by Sjögren's syndrome, idiopathic pulmonary fibrosis, rheumatoid arthritis, severe dry eye, open-angle glaucoma, and keratoconus. She reported ocular pain in the left eye that was refractory to multiple treatments including ocular lubricants or autologous serum eye drops applied hourly, systemic NSAIDs, and opioids. The pain specialist, in accordance with her general practitioner, did not recommend additional medications, as a consequence of the many patient comorbidities and referred intolerance to gabapentin. At enrollment, the VAS ocular pain score for the left eye was 6/10 and the OSDI score was 100/100. The patient was treated with 0.1 mg/mL fosaprepitant eye drops in PBS in the left eye, first 3 times a day for 3 days, and subsequently 2 times a day for 18 days. The experimental drug was administered in addition to the existing medications.

2.1.2. Case #2

The second case was an 82-year-old woman suffering from Foster stage II mucous membrane pemphigoid and severe ocular pain (VAS score 10/10). She presented with severe blepharitis, cataracts, glaucoma in both eyes, punctate keratopathy in the right eye, and a central descemetocele in the left eye. Her symptoms were resistant to paracetamol, tapentadol, anti-inflammatory eye drops, multiple systemic immunosuppressors (including methotrexate and cyclophosphamide), topical/systemic corticosteroids, and hourly lubricant instillation. The

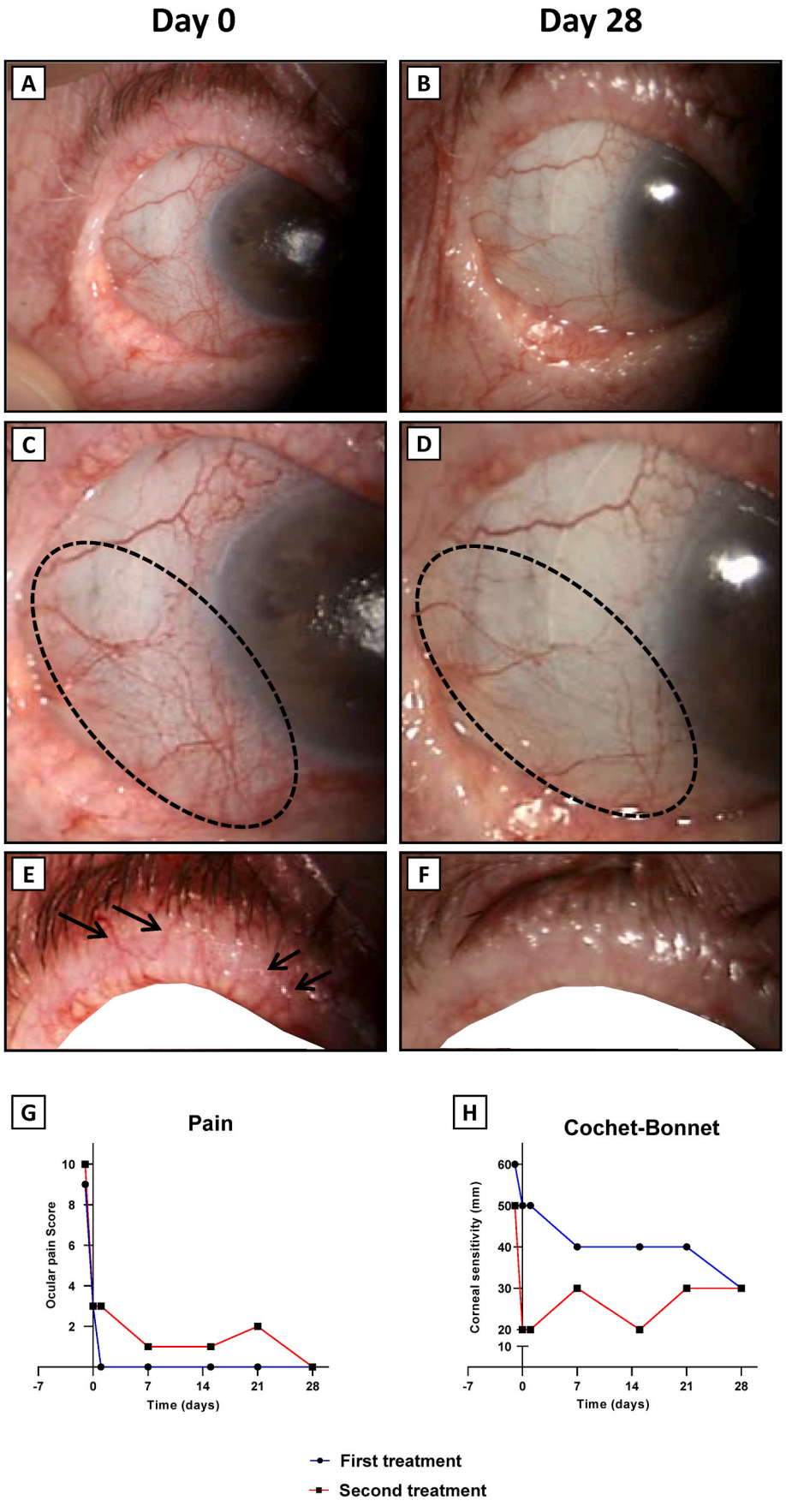

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Fig. 2. Clinical outcomes and biomicroscopy result in case #2.
Biomicroscopy pictures reveal that fosaprepitant does not exert side effects after 4 weeks of treatment (B) and improves clinical outcomes to the day of enrollment (A). Topical fosaprepitant effectively reduces corneal inflammation (D) and conjunctival hyperemia (F) compared to baseline (C–E). The hatched area in figures C–D highlight a focus on corneal hyperemia before (C) and after (D) treatment. VAS questionnaire shows that fosaprepitant is effective in reducing ocular pain in both two administrations (G). Corneal sensitivity measurement revealed that NK1R antagonism does not significantly affect corneal sensitivity during the first treatment, despite the second administration (H). The data were analyzed by nonparametric Spearman's rank correlation.

patient was started on a 4-week course of 10 mg/mL fosaprepitant dissolved in PBS under sterile conditions, administered 6 times per day in the right eye, in addition to the existing medications. After one year, ocular pain relapsed (VAS score 10/10) and she was re-treated following the same protocol.

2.1.3. Case #3

The third patient was an 18-year-old girl suffering from fibromyalgia and biopsy-proven small fiber neuropathy. The patient complained of constant bilateral ocular pain, which interfered with sleep, and was graded 7/10 on VAS. In vivo confocal microscopy revealed severe corneal neuropathy and numerous neuromas (Fig. 3A and B). She had been previously treated with systemic gabapentin, duloxetine, folic acid, and food supplements (ginger) to no avail. Hourly lubricant instillation, topical corticosteroids, and NSAIDs were not effective. Fosaprepitant eye drops (10 mg/mL in PBS) were administered as follows: 4 times a day for 4 days and 3 times a day for the following 3 days; 2 times a day during the second week; 1 time a day during the third week; 1 time every other day during the fourth week. The patient was then followed-up for 3 more weeks. After 3 weeks, the pain gradually recurred (VAS score from 4/10 to 7/10) and the patient was treated with saline solution 3 times a day for 1 week, with no improvement in ocular pain (VAS score 9/10). She has then switched to fosaprepitant 10 mg/mL topical treatment 3 times a day for 3 weeks.

3. Results

All patients completed the treatment with no side effects. After treatment was interrupted, all the 3 cases reported a progressive increase in ocular pain, and treatment was repeated in cases 2 and 3. Case 1 was lost at follow-up. The IOP was measured before and after treatment and remained within normal limits in all three cases.

3.1. Case #1

Before treatment, patient 1 showed punctate keratopathy (Fig. 1A), as well as marked conjunctival hyperemia (Fig. 1C). After 3 weeks of 0.1 mg/mL topical fosaprepitant, we observed improved corneal epitheliopathy (Fig. 1B) and a clinically evident reduction of conjunctival hyperemia (Fig. 1D). Moreover, we found a modest reduction in corneal sensitivity before and after treatment (from 45 to 40 mm with Cochet-Bonnet, Figure G). During treatment, the patient reported total resolution of ocular pain (VAS score from 6/10 to 0/10), and a 25 % reduction in ocular discomfort (OSDI score from 100/100 to 75/100) (Figures E–F).

3.2. Case #2

At enrollment, patient 2 presented inflammation, and conjunctival hyperemia (Fig. 2A, C, 2E). After 4 weeks of treatment with 10 mg/mL topical fosaprepitant, the patient also reported a significant reduction in ocular pain (Fig. 2G; $r = -0.8018$; $P < 0.05$) without showing changes in corneal sensitivity (Fig. 2H; $r = 0$; P = ns). We also observed reduced conjunctival hyperemia (Fig. 2B, D, 2F). Following re-treatment, she reported reduced ocular pain (Fig. 2G; $r = -0.8729$; $P < 0.05$) and reduced corneal sensitivity (Fig. 2H; $r = -0\ 0.9543$; $P < 0.01$).

3.3. Case #3

Before and after treatment, patient 3 showed no detectable ocular surface anomalies in both eyes (Fig. 3C and D), at the slit-lamp. However, confocal microscopy revealed multiple neuromas and severely reduced density of the corneal sub-basal nerve plexus (Fig. 3A and B). Pain was rapidly abated after the first administration, as measured with VAS (Fig. 3E; $P < 0.001$), and OSDI score (Fig. 3F; $P < 0.001$). This was further confirmed by the number of daily applications of lubricants, which decreased significantly (Fig. 3G; $P < 0.01$). Interestingly, no reduction in corneal sensitivity was observed (Fig. 3H; P = ns). Conversely, after treatment withdrawal, or placebo administration, ocular pain relapsed, as measured with VAS (Fig. 3E; $P < 0.01$) and OSDI scores (Fig. 3F; $P < 0.01$). The frequency of lubricant instillation increased to pre-treatment values during placebo (P) administration (Fig. 3G). However, subsequent re-administration of fosaprepitant reversed the trend again, leading to a reduced OSDI score (Fig. 3F; $P < 0.05$) and diminished frequency of lubricant administration (Fig. 3G; $P < 0.01$). Accordingly, the VAS score decreased significantly (Fig. 3E; $P < 0.01$) compared to placebo administration.

4. Discussion

Herein, we presented three clinical cases of patients affected with chronic, resistant ocular pain. They were treated topically with the NK1R antagonist fosaprepitant through a compassionate use program.

The drug concentration was chosen based on our previous works demonstrating that 10 mg/mL fosaprepitant was not toxic for the ocular surface and promptly induced corneal analgesia.[10] For Case 1, we provided a lower fosaprepitant dosage (0.1 mg/mL) as an additional safety margin. Therefore, after excluding any side effects, the concentration was increased to the most effective (10 mg/mL) in cases 2 and 3.

Our data show that topical administration of fosaprepitant eye drops reduces ocular surface pain and discomfort without causing obvious side effects. The follow-up observation of cases 2 and 3 showed that fosaprepitant discontinuation caused a variable pain-free period after which pain recurred. In patient 2, recurrence occurred after one year, while in patient 3 after 3 weeks. This discrepancy may be due to the different diseases affecting patients (i.e: ocular cicatritial pemphigoid for case 2 and fibromyalgia with peripheral sensory neuropathy for case 3).

Besides reducing pain, fosaprepitant also improved corneal epitheliopathy and reduced conjunctival hyperemia, which are typically associated with ocular pain[8,13] in two patients. These data are relevant since SP is a cardinal mediator of neuroinflammation in the cornea, and promotes hemangiogensis, lymphangiogenesis, and leukocyte recruitment/activation.[7] Therefore, blockade of SP activity by means of fosaprepitant results in a potent anti-inflammatory activity, which is demonstrated by our finding of reduced hyperemia.[10,15] Moreover, the decreased number of lubricant instillations in case 3 is an additional, indirect indicator of clinical improvement. Interestingly, and differently from topical anesthetics, corneal sensitivity was not substantially affected in 2/3 of cases and persisted to some level in 3/3 of cases. The reduction of corneal sensitivity was mild and not significant, with the exception of the second administration of Case 2. While additional studies are needed for a definitive confirmation, in this case series corneal sensitivity was not reduced overall. We believe this has relevant clinical implications because long-term suppression of corneal sensitivity results in neurotrophic keratopathy,[14] which makes chronic use of

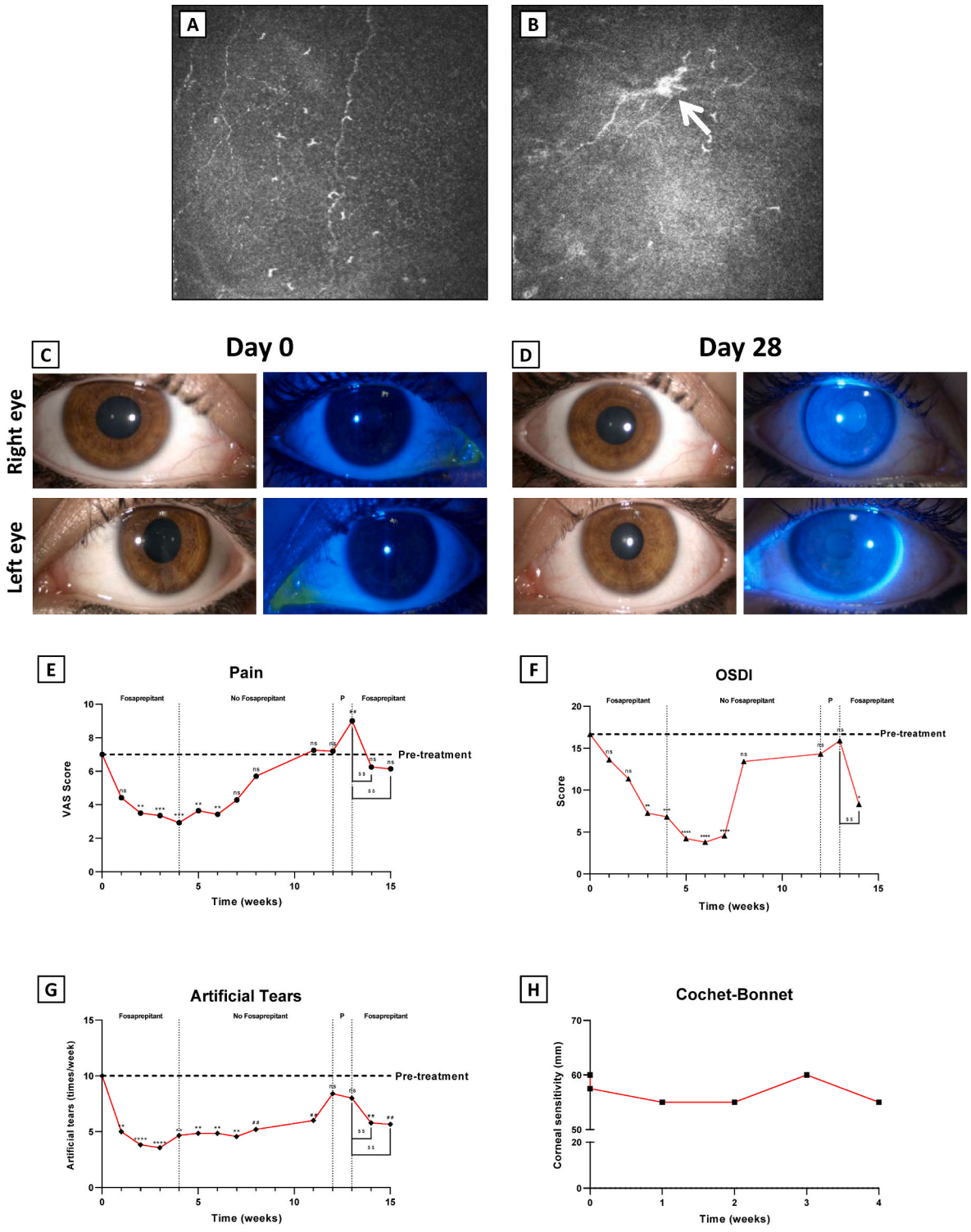

Fig. 3. Clinical outcomes and biomicroscopy result in case #3.
Confocal microscopy images showing the presence of numerous neuromas in patient 3 (A–B). Slit-lamp biomicroscopy pictures reveal no ocular surface defects before (C) and after (D) topical instillation with fosaprepitant. Figure B shows a high magnification detail of neuromas (arrow) detected in case 3. VAS and OSDI questionnaires demonstrate the beneficial effect of both drugs during administrations, which is reverted after suspension and placebo (P) application (E–F). Graph G shows that artificial tear eye drops application decreases during the fosaprepitant treatments, remaining stable during drug suspension and reverting during the use of placebo (P). Cochet-Bonnet measurements exhibit stable corneal sensitivity throughout fosaprepitant instillation. Statistical analysis was performed using the Mann–Whitney test (# = placebo vs. pre-treatment; $ = placebo vs. fosaprepitant), and the Kruskal-Wallis test followed Dunn's method (* = time point vs. pre-treatment). $^{\#\#}P < 0.01$; $^{\$\$}P < 0.01$; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

anesthetics unsafe.

5. Conclusions

Topical administration of fosaprepitant ameliorated chronic ocular pain and clinical symptoms in three patients with chronic pain due to inflammatory ocular surface diseases. This study provides preliminary evidence for the safety and efficacy of NK1R antagonists in the treatment of ocular pain and inflammation. Further studies on a larger cohort of patients are needed to confirm the positive effects of fosaprepitant and identify a standardized frequency of administration.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Mehra D, Cohen NK, Galor A. Ocular surface pain: a NarrativeReview. *Ophthalmol Ther*. Sep. 2020;9(3):1. https://doi.org/10.1007/S40123-020-00263-9.
2. Zdebik N, Zdebik A, Bogusławska J, Przeździecka-Dołyk J, Turno-Kręcicka A. Fibromyalgia syndrome and the eye-A review. *Surv Ophthalmol*. Jan. 2021;66(1):132–137. https://doi.org/10.1016/J.SURVOPHTHAL.2020.05.006.
3. Rigas B, Huang W, Honkanen R. NSAID-induced corneal melt: clinical importance, pathogenesis, and risk mitigation. *Surv Ophthalmol*. Jan. 2020;65(1):1–11. https://doi.org/10.1016/J.SURVOPHTHAL.2019.07.001.
4. Tripathi RC, Parapuram SK, Tripathi BJ, Zhong Y, Chalam KV. Corticosteroids and glaucoma risk. *Drugs Aging*. 1999;15(6):439–450. https://doi.org/10.2165/00002512-199915060-00004.
5. Jacobs DS. Diagnosis and treatment of ocular pain: the ophthalmologist's perspective. *Curr Ophthalmol Rep*. Dec. 2017;5(4):271. https://doi.org/10.1007/S40135-017-0152-1.
6. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. *Biochem Pharmacol*. 2020;180(Oct). https://doi.org/10.1016/J.BCP.2020.114147.
7. Lasagni Vitar RM, Rama P, Ferrari G. The two-faced effects of nerves and neuropeptides in corneal diseases. *Prog Retin Eye Res*. Jan. 2022;86. https://doi.org/10.1016/J.PRETEYERES.2021.100974.
8. Barbariga M, Fonteyne P, Ostadreza M, Bignami F, Rama P, Ferrari G. Substance P modulation of human and murine corneal neovascularization. *Invest Ophthalmol Vis Sci*. Mar. 2018;59(3):1305–1312. https://doi.org/10.1167/IOVS.17-23198.
9. Singh RB, et al. Modulating the tachykinin: role of substance P and neurokinin receptor expression in ocular surface disorders. *Ocul Surf*. Jul. 2022;25:142–153. https://doi.org/10.1016/J.JTOS.2022.06.007.
10. Vitar RML, Barbariga M, Fonteyne P, Bignami F, Rama P, Ferrari G. Modulating ocular surface pain through neurokinin-1 receptor blockade. *Invest Ophthalmol Vis Sci*. Mar. 2021;62(3). https://doi.org/10.1167/IOVS.62.3.26.
11. Bignami F, Lorusso A, Rama P, Ferrari G. Growth inhibition of formed corneal neovascularization following Fosaprepitant treatment. *Acta Ophthalmol*. Nov. 2017;95(7):e641–e648. https://doi.org/10.1111/AOS.13304.
12. Aapro M, Carides A, Rapoport BL, Schmoll H-J, Zhang L, Warr D. Aprepitant and fosaprepitant: a 10-year review of efficacy and safety. *Oncol*. Apr. 2015;20(4):450–458. https://doi.org/10.1634/THEONCOLOGIST.2014-0229.
13. Belmonte C. Pain, dryness, and itch sensations in eye surface disorders are defined by a balance between inflammation and sensory nerve injury. *Cornea*. Nov. 2019;38(Suppl 1):S11–S24. https://doi.org/10.1097/ICO.0000000000002116.
14. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. Mar. 2014;8:571–579. https://doi.org/10.2147/OPTH.S45921.
15. Vitar RML, Bonelli F, Atay A, et al. Topical neurokinin-1 receptor antagonist Fosaprepitant ameliorates ocular graft-versus-host disease in a preclinical mouse model. *Exp Eye Res*. Nov. 2021;212, 108825. https://doi.org/10.1016/j.exer.2021.108825.