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METHODS

Topical nepafenac 0.1% or 0.3% for the treatment of central serous chorioretinopathy: A case series of chronic and recurrent disease and review of the literature

Ishani Hariprasad[1], Leonard V. Messner[2], Lincoln T. Shaw[3*], Chandani A. Bansal[4], Sidney A. Schechet[5] and Janette Pérez[2]

[1]University of Chicago Laboratory Schools, Chicago, IL, United States
[2]Illinois Eye Institute, Chicago, IL, United States
[3]Department of Ophthalmology, The University of Chicago, Chicago, IL, United States
[4]The University of Texas at Austin, Austin, TX, United States
[5]Elman Retina Group, Baltimore, MD, United States

***Correspondence:**
Lincoln T. Shaw,
lincolnshawmd@gmail.com

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Central serous chorioretinopathy (CSCR) is a disease involving leakage of serous fluid through the retinal pigment epithelium, resulting in neurosensory retinal detachment. The majority of acute CSCR cases resolve spontaneously. However, treatment options for chronic and recurrent cases are lacking. In this case series, topical nepafenac 0.1% and 0.3% was investigated as novel treatments for chronic and recurrent CSCR. We performed a retrospective case series analysis of six patients diagnosed with chronic recurrent CSCR. Data from medical records of patients were collected, including age range, gender, subjective complaints, Snellen visual acuity (VA), clinical eye examination, central macular thickness (CMT) on optical coherence tomography, prior treatments, time of follow-up, and time to resolution of CSCR. The six cases of chronic and recurrent CSCR in this study were treated with 0.1% and/or 0.3% topical nepafenac. The mean age of the six cases was 52 years. There was an average gain in the vision of 2.5 lines in Snellen VA, and a final Snellen VA of 20/20 was achieved in each case. The average time to complete the resolution of CSCR was 3.33 months. The decrease in CMT ranged from 105 μm to 507 μm, with an average decrease of 240 μm, and subretinal fluid resolved completely in all six cases.

Keywords: central serous chorioretinopathy, nepafenac, NSAID, COX-2 inhibition, topical therapy

Introduction

Central chorioretinopathy (CSCR) is a disease involving leakage of serous fluid through the retinal pigment epithelium (RPE) that results in neurosensory macular retinal detachment. The fluid accumulation leads to blurring and distortion of central vision, as the disease typically involves the macula (1). While the pathogenesis of CSCR is poorly understood, known risk factors include the use of glucocorticoids (2–5) or elevated levels of endogenous corticosteroids. (6) Additional risk factors speculated for the development of CSCR include hypertension, (5, 7) male gender, (8, 9) pregnancy, (7, 10) and type A personality, although these associations are more controversial (11).

Central serous chorioretinopathy may occur in an acute or chronic setting. Although arbitrary, most studies classify the disease as chronic if it persists for longer than 3 (12–14) to 6 (15) months. Acute CSCR is typically self-limited, and 80–90% of CSCR cases are thought to self-resolve with no long-term visual sequelae. Chronic and recurrent CSCR, however, can result in widespread damage to the RPE, which is also referred to as diffuse retinal pigment epitheliopathy (DRPE) (1). Patients with DRPE have long-term subretinal

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fluid (SRF) that cannot be reabsorbed due to dysfunction of the RPE and choroid. (16) In addition, up to 30–50% of CSCR patients have a recurrence of the SRF within 1 year (17).

It is difficult to assess the efficacy of treatment options for CSCR due to its tendency to self-resolve in the acute setting. Various treatment options have been proposed, and a review conducted by Nicholson et al. in 2013 discusses the treatment options and rates the quality of evidence, as defined by the US Preventive Services Task Force (good, fair, or poor-quality evidence). Treatments with good evidence include discontinuation of steroids, laser photocoagulation, and photodynamic therapy. Treatments with fair evidence include observation and risk-factor modification. Many common treatments, however, have poor evidence to support their use, including *Helicobacter pylori* treatment, anti-glucocorticosteroids, carbonic anhydrase inhibitors, anti-vascular endothelial growth factor agents, aspirin, diode micropulse laser, and transpupillary thermotherapy (1).

Recent studies regarding other pharmacologic agents for the treatment of CSCR, including eplerenone, (18, 19) rifampin, (20) spironolactone, (21) and brinzolamide (22) have promising results. Nepafenac is a topical non-steroidal anti-inflammatory drug (NSAID) available in 0.1% (Nevanac, Alcon, Fort Worth, TX) and 0.3% formulations (Ilevro, Alcon, Fort Worth, TX, USA) used in the treatment of pain and inflammation after cataract surgery (23, 24). Nepafenac has been shown to be a safe and effective treatment for chronic cystoid macular edema in patients who have a steroid-induced increase in intraocular pressure secondary to topical steroidal agents (25). Our case series highlights the potential therapeutic benefits of the use of nepafenac 0.1 and 0.3% solutions for the treatment of chronic and recurrent CSCR.

Research elaborations

We performed a retrospective case series of six patients who were diagnosed with chronic or recurrent CSCR and managed at the University of Chicago Medical Center. Patient data were obtained through written paper charts and Epic electronic medical records. The patients included in the research were serially followed from their initial visit to February 23, 2015. Medical records of patients were reviewed and assessed for changes in various measures, including subjective complaints, Snellen visual acuity (VA), clinical eye examination, and central macular thickness (CMT) (in micrometers) based on optical coherence tomography (OCT). Additional data collected included age, gender, prior treatment, time of follow-up, and time to resolution of CSCR from the onset of presentation.

Cases

Case 1

A male in his early 40 s presented after noticing wavy lines and blurred vision in the right eye for 3 weeks. He reported similar episodes in the past. The patient was experiencing high levels of stress. The patient's initial VA in the affected eye was 20/25-3 and the macular OCT scan revealed SRF with a CMT of 349 μm. The patient was diagnosed with CSCR and was initiated with a nepafenac 0.3% solution once daily in the right eye. At his 2-month follow-up visit, there was a complete resolution of the SRF in the right eye and his VA improved from 20/25-3 to 20/20.

Case 2

A female in her early 70 s was initially misdiagnosed with exudative macular degeneration in the left eye. She presented 11 months after her primary diagnosis for a second opinion. She presented with an initial VA of 20/40 in the left eye, SRF on clinical examination, and OCT with a CMT of 369 μm. She was diagnosed with CSCR and 3 months after nepafenac 0.1% was initiated three times a day, her SRF completely resolved, her VA improved to 20/25, and her CMT decreased to 190 μm. Nepafenac was then tapered gradually to once daily by the 34-months visit. At 54-month follow-up, after 4.5 years of stability, she presented with recurrence of the disease with an increase in CMT to 400 μm. At the time, nepafenac 0.3% was available and she was started on once-daily dosing. Two months after nepafenac 0.3% was initiated, her SRF resolved, VA returned to 20/20-2, and her CMT on OCT improved to 230 μm.

Case 3

A female in her early 50 s with a history of primary open-angle glaucoma was referred for management of presumed polypoidal choroidal vasculopathy of the left eye. Despite monthly intravitreal bevacizumab injections for 6 months, she continued to experience blurred vision. She was diagnosed with chronic CSCR upon presentation to our service and, after 8.5 months of treatment with nepafenac 0.1% TID, resolution of the SRF and a significant improvement in VA was achieved. Nepafenac 0.1% TID was then switched to 0.3% once daily when it became commercially available, and this was maintained for 1.5 months and then tapered off. One month after discontinuation of nepafenac 0.3%, a recurrence of symptoms with extrafoveal SRF was identified. Nepafenac 0.3% once daily was reinitiated. Resolution of SRF with an improvement of vision was achieved again within 2 months.

Case 4

A male in his mid-30 s presented with a 3 days history of right eye blurriness. He noted that the symptoms

were especially apparent when transitioning between light and dark environments. He reported similar episodes in the past. The presenting VA of the right eye was 20/20. SRF was present on clinical examination and OCT with a CMT of 579 μm. The patient was diagnosed with CSCR and was started on nepafenac 0.1% three times daily. At his 2-month follow-up visit, the patient reported symptomatic improvement, with a stable VA of 20/20-1. CMT had improved from 579 μm to 320 μm. The patient was instructed to continue taking nepafenac 0.1% three times daily until the bottle ran out.

Case 5

A female in her mid-70 s was diagnosed with CSCR and her management involved observation for 7 months without any resolution of SRF or symptoms. Her VA was stable at 20/50. Three to four months after the initiation of nepafenac 0.1% TID, SRF was completely resolved and there was some improvement in VA. Nepafenac was gradually tapered to once daily. Seven months later, a recurrence of SRF was noted. Nepafenac was increased back to TID dosing, which resulted in a decrease in SRF and improvement in vision in 2.5 months. The patient was stable on nepafenac 0.1% BID for 34 months when a second recurrence was noted. She was switched to nepafenac 0.3% once daily at the time, and 8 months later, her SRF had resolved and her VA had improved to 20/20 at the last follow-up.

Case 6

A male in his late 30 s presented with a 3-month history of blurred vision in the left eye. He reported similar episodes in the past. Initial VA was 20/30-3, and examination showed central SRF and OCT with a CMT of 525 μm. The patient was observed initially for 2 months, with a minimal improvement of the SRF (CMT 427 μm) and persistent VA of 20/30-3. Regarding treatment, 0.3% nepafenac was started daily, and at the 1-month follow-up visit after starting nepafenac, his SRF completely resolved and CMT improved to 227 μm (**Figure 1**). His VA improved to 20/20 and he discontinued nepafenac soon after. His vision was stable at 20/20 at the 2.5-year-follow-up visit.

Results

The six cases of CSCR in this study were all treated with topical 0.1 or 0.3% nepafenac. **Table 1** shows demographic and clinical data about each of the six cases. The mean age of the six cases was 52 years. There was an average gain in a vision of about 2.5 lines in Snellen VA. SRF was completely resolved all six cases, with an ending VA of 20/20 in each case. The average time to complete the resolution of CSCR was 3.33 months. **Figure 2** shows a decrease in CMT in the treated eye over the course of the treatment period for each of the six cases. The decrease in CMT in the treated eye ranged from 105 to 507 μm, with an average decrease of 240 μm. No ocular side effects or adverse events were reported with nepafenac use.

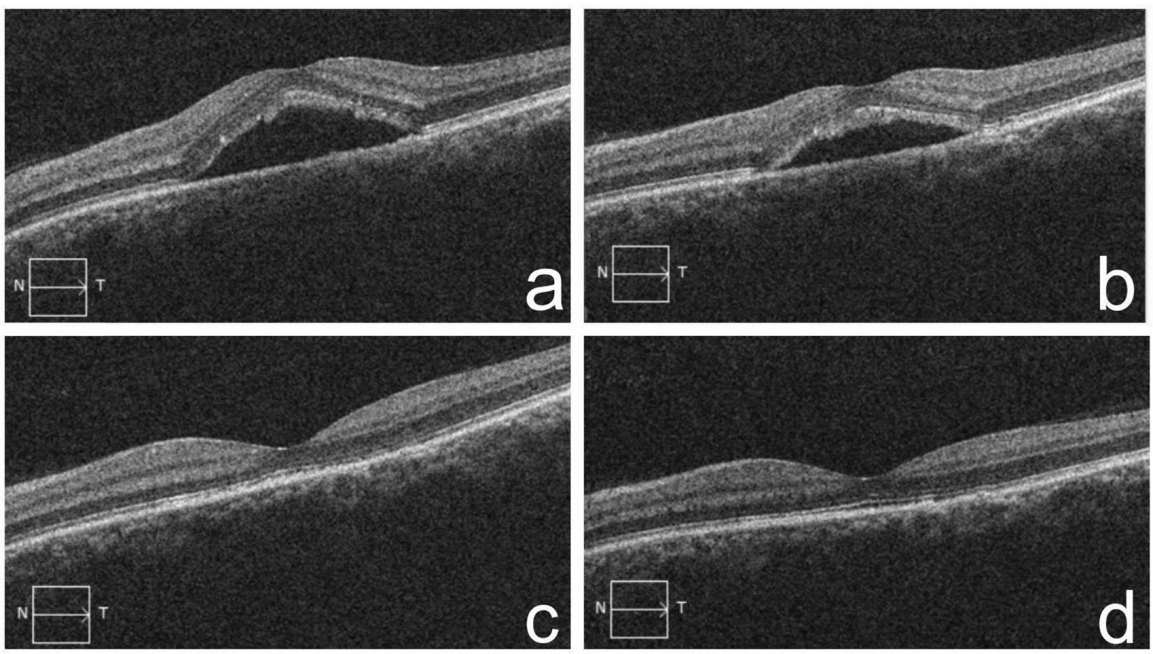

FIGURE 1 | OCT images from case 6. A male in his late 30 s presented with a 3 months history of blurred vision in the left eye. **(a)** Initial OCT revealed SRF with CMT of 525 μm. Two months after initial evaluation, **(b)** the SRF improved and CMT decreased to 427 μm. One month after initiating 0.3% topical nepafenac daily, **(c)** his SRF resolved completely, with a CMT of 227 μm. Furthermore, 2.5 years after initial presentation, **(d)** his SRF did not recur, and CMT remained stable at 237 μm.

TABLE 1 | Demographic and clinical characteristics of cases.

Case #	1	2	3	4	5	6
Age range at initial presentation	40–45	70–75	50–55	35–40	70–75	35–40
Gender	Male	Female	Female	Male	Female	Male
Type of CSCR	Chronic, recurrent	Chronic, recurrent	Chronic, recurrent	Chronic, recurrent	Chronic, recurrent	Chronic, recurrent
Topical NSAID used	Nepafenac 0.3%	Nepafenac 0.1% and Nepafenac 0.3%	Nepafenac 0.1% and Nepafenac 0.3%	Nepafenac 0.1%	Nepafenac 0.1% and Nepafenac 0.3%	Nepafenac 0.3%
Other treatments	None	None	Intravitreal bevacizumab	None	None	None
Total follow-up time	17 months	62.5 months	23 months	2 months	42 months	32 months
Complete resolution of serous retinal detachment at final visit	Yes	Yes	Yes	Yes	Yes	Yes
Number of months to resolution	2.0	3.0	8.5	2.0	3.5	1.0
Initial Snellen visual acuity	20/25-3	20/40	20/70-1	20/20	20/50	20/30-3
Final Snellen visual acuity	20/20	20/20-2	20/20	20/20-2	20/20-2	20/20
Initial central macular thickness (μm)	349	369	723	579	400	525
Final central macular thickness (μm)	233	230	216	320	280	227

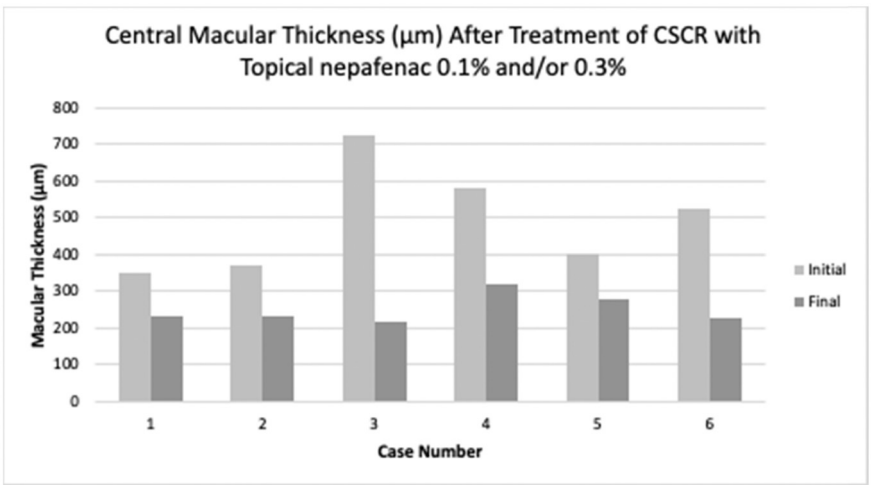

FIGURE 2 | Decrease in central macular thickness in the treated eye.

Conclusion

Nepafenac is an NSAID medication that is a prodrug of amfenac. Amfenac is a non-steroidal analgesic and anti-inflammatory drug that is a potent inhibitor of both the cyclooxygenase (COX) 1 and 2 pathways, as opposed to traditional ophthalmic NSAIDs such as ketorolac, which primarily inhibit the COX1 pathway. Nepefanac has the additional benefit of existing in the prodrug state, which results in a less polar molecule to allow better penetration of the corneal epithelium than other NSAID preparations, including ketorolac, diclofenac, and bromfenac. In rabbit models, nepafenac has been shown to readily distribute to all ocular tissues, including aqueous humor, iris, ciliary body, retina, and choroid (26). The nepafenac prodrug then undergoes hydrolysis in tissues to become the active amfenac molecule, which strongly inhibits proinflammatory eicosanoids, such as prostaglandins and leukotrienes. Interestingly, the retina and choroid have been shown in rabbit models as the most active tissues with regard to the hydrolytic activity of the nepafenac molecule in its active form (26).

Cystoid macular edema owing to uveitis and diabetic retinopathy has been reported to show improvement with topical nepafenac (27–29). We believe the advantages of increased ocular penetration and both COX1 and COX2 pathways' inhibition allow nepafenac to better control ophthalmic inflammatory pathways, leading to CSCR, than other commercially available ophthalmic NSAIDs. Furthermore, multiple cases of CSCR or CSCR-like serous detachments have been linked with topical prostaglandin analogs, such as latanoprost, (30–32) which suggests that

the vaso-constrictive effects of COX inhibition through prostaglandin pathways of the choriocapillaris may be important in reducing capillary leakage in CSCR. These are changes that are likely better targeted by nepafenac given its activity in both the COX1 and COX2 pathways.

As CSCR self-resolves in 80% of patients, (33) treatments are difficult to study in clinical trials because the disease's natural history is often short and self-limiting. However, treatment methods that are non-invasive and allow for faster time to resolution or treatment of chronic and/or recurrent episodes of CSCR still have potential therapeutic benefits for many patients.

Bahadorani et al. (34) reported a series of 14 eyes treated with topical 0.09% bromfenac, 0.1% nepafenac, or 0.3% nepafenac with promising results, suggesting a faster resolution of SRF compared to 13 control eyes over a follow-up period of a few weeks. Similarly, Alkin et al. (35) reported a series of 17 eyes treated with 0.1% nepafenac compared to 14 eyes in the control group, which were observed. At 6 months of follow-up, 14 eyes (82.3%) of the treatment group had complete resolution of SRF compared to 6 eyes (42.8%) of the control group ($p = 0.02$) (35). Both studies reported similar final visual acuities between the treatment and control groups, and neither study reported any adverse events related to topical nepafenac use. Similarly, it is our experience that topical nepafenac is very safe and well tolerated.

We believe that nepafenac, dosed as a 0.1% solution three times daily or a 0.3% solution once daily, is a potentially safe and effective therapeutic option for patients with chronic or recurrent CSCR.

Author contributions

IH: substantial contributions to the design of the work and the acquisition of the data. LS and JP: substantial contribution to the interpretation of the data, drafting of the work, and revisions to the final submission. LM, CB, and SS: considerable contribution to the review of the manuscript. All authors revised the work and gave final approval of the version published.

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