

Is There A Role for Intravitreal Pharmacotherapy in the Treatment of Acute Nonarteritic Ischemic Optic Neuropathy?

Melih Parlak, Ali Osman Saatci

Melih Parlak, Klinikum Konstanz, Department of Ophthalmology, Konstanz, Germany

Ali Osman Saatci, Professor, Dokuz Eylul University Medical School, Ophthalmology Department, Izmir, Turkey

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Correspondence to: Ali Osman Saatci, Mustafa Kemal Sahil Bulvarı, No: 73, A Blok D: 9, 35320 Narlıdere/Izmir, Turkey.

Email: osman.saatci@yahoo.com

Telephone: +905327437071

Received: June 19, 2016

Revised: August 14, 2016

Accepted: August 17, 2016

Published online: December 31, 2016

ABSTRACT

AIM: To review the safety and efficacy of intravitreal pharmacotherapy in the treatment of acute nonarteritic anterior ischemic optic neuropathy (NAION).

CONTEXT: Early reports on acute NAION indicated that no therapy was effective enough to improve the natural outcome of the disease. Till now on, a large number of therapeutic modalities have been tried but none has turned out to be the gold standard. Today, intravitreal pharmacotherapy, which provides sufficient vitreous drug concentrations in the eye is widely employed in various retinal disorders successfully.

METHOD: A thorough literature search was conducted in May 2016 to retrieve all manuscripts related to acute NAION treatment and we particularly focused on manuscripts about intravitreal therapy.

CONCLUSION: Today, the role of intravitreal pharmacotherapy in NAION is still not well-established. It is evident that only randomized-controlled trials can give a scientific answer and clarify the place of intravitreal pharmacotherapy in the treatment of acute NAION.

Key words: Anti-VEGF; Erythropoietin; Fasudil; Ischemic optic neuropathy; Ozurdex; siRNA; Triamcinolone

© 2016 The Author(s). Published by ACT Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Parlak M, Saatci AO. Is There A Role for Intravitreal Pharmacotherapy in the Treatment of Acute Nonarteritic Ischemic Optic Neuropathy? *International Journal of Ophthalmic Research* 2016; 2(4): 192-197 Available from: URL: <http://www.ghrnet.org/index.php/ijor/article/view/1762>

INTRODUCTION

Acute nonarteritic ischemic optic neuropathy (NAION) is an important cause of impaired vision or blindness in elderly population^[1]. It is the most common optic neuropathy seen after the fifth decade with its estimated annual incidence between 2.9 and 10.2 per 100 000 population^[2-4]. It is typical characterized by a painless, monocular loss of vision, occurring over hours to days. Hayreh *et al*^[5] reported that the visual disturbance was often noticed upon awakening, most likely due to nocturnal hypotension in addition to already present systemic abnormalities such as hypertension and diabetes mellitus.

Inadequate perfusion of the optic nerve head deriving from the short posterior ciliary vessel plexus is the key mechanism in the development of acute NAION^[6]. However, a prevalent anatomic finding of a small or absent physiologic cup, which is common known as 'disc at risk', seems to play also an important role^[6,7]. In combination with other atherogenic and vasoconstrictive risk factors such as hypertension, sleep apnea syndrome, diabetes, dyslipidaemia an ischemic nerve fiber swelling in a tight -looking disc leads to a vicious cycle of ischemia and disc edema^[1,2,6-9].

Presenting visual acuity in acute NAION can vary from 20/20 to no perception of light. Colour vision is often in accordance with the visual acuity whereas visual field defects may show a considerable discrepancy. In typical cases, the visual acuity worsens over the first

two weeks and then may remain stable or show a slight improvement or deteriorate. In majority, visual field loss is an inferior altitudinal defect but any type of field defect related to the axonal damage may be present. Visual acuity or perimetric findings do not appear to differ any more following the resolution of the disc edema^[10,11]. In the ischemic optic neuropathy decompression trial spontaneous visual improvement was seen in 45% of the patients within six months of the disease onset, no visual improvement was seen in 45% of the patients and even further visual decline was noted in 12% of the cases^[10].

There is still no well-established treatment for acute NAION despite ongoing extensive basic and clinical research. Several treatment modalities, targeting decompression, neuro protection or anticoagulation were tried but no convincing treatment effect could be demonstrated^[9].

Nowadays, intravitreal pharmacotherapy plays a crucial role in the treatment of many entities. There were several case series and uncontrolled trials regarding the intravitreal drug administration utilizing a multitude of agents with mixed results for the treatment of acute NAION. This study reviews the therapeutic value of these intravitreal agents as a treatment option in acute NAION.

INTRAVITREALLY ADMINISTERED AGENTS IN ACUTE NAION

Corticosteroids (Triamcinolone acetonide, Dexamethasone implant)

Optic disc edema in acute NAION develops due to axoplasmic flow stasis and capillary leakage. Additionally, an inflammatory response has been reported in rodent NAION models, similar to other central nerve system ischaemic infarcts^[12,13]. Steroids are advocated as they can decrease the capillary permeability, suppress the inflammation and thereby facilitate the resolution of optic disc edema. In fact, systemic methylprednisolone administration was shown to have a positive effect on retinal ganglion cell survival^[14]. Hayreh and Zimmerman^[15] investigated the visual outcome of oral 80 mg prednisolone in a large cohort of 613 acute NAION patients. They showed that treating the eyes with acute NAION with in the first 2 weeks after the onset with systemic steroids, resulted in a significantly higher probability of improvement in visual acuity and visual field, compared to untreated patients. However, systemic corticosteroid administration is fraught with serious systemic complications especially in an elderly population with already known comorbidities. As intravitreal administration of triamcinolone acetonide and/or dexamethasone implant directly affects the target tissue the therapeutic effect is achieved without inducing any systemic side effect. However, intraocular pressure rise and cataract formation are the downsides of the intravitreal steroid therapy.

Jonas *et al*^[16] reported three cases with acute NAION, who were intravitreally treated with a high dose of 20 mg triamcinolone acetonide. No major change in the visual field was observed in all three cases. While visual acuity slightly improved in two of the cases, the remaining patient experienced a visual decline. They suggested that the clinical benefit of high dose triamcinolone was limited when compared to benefit occurred in patients with diabetic papillopathy. Kaderli and associates^[17] presented a small case-control study, where four eyes with acute NAION were treated with intravitreal 4 mg triamcinolone. The results were compared with six acute NAION patients, who received no treatment. In eyes treated with intravitreal triamcinolone they observed a rapid resolution of disc

swelling and a relatively good visual recovery. The improvement of visual acuity was 6.2 and 1.3 ETDRS lines with and without intravitreal triamcinolone administration respectively. In both groups, a meaningful visual field recovery could not be achieved. Similar results were reported by Yaman *et al*, who treated four consecutive acute NAION patients with 4 mg intravitreal triamcinolone who had a disease duration of ten days or less. During the follow-up of at least three months, all patients experienced a visual gain and even two of them gained three or more Snellen lines^[18]. In another case-control study, Radoi *et al*^[19] reviewed their 36 patients with acute NAION and analysed them in two subgroups: Twenty-one cases received a single intravitreal triamcinolone injection, while 15 patients were followed without any treatment. Six months after, a significantly higher proportion of patients experienced a visual acuity improvement in the treated group (71% vs 13%). Visual improvement of more than three lines was more commonly observed in the treated patients when compared to no-treatment group. Visual field improvement was observed in the treated group whereas visual fields remained either stable or deteriorated in no-treatment group. All injected patients were treated with topical brinzolamide and the intraocular pressure stayed within normal range in the treated eyes during the follow-up.

Ozurdex (Allergan Inc., Irvine, CA, USA) is a biodegradable dexamethasone sustained-release intravitreal implant delivering dexamethasone directly within the vitreous cavity. Because of its anti-inflammatory properties with a favourable side-effect profile, it became an important treatment option for the macular edema in patients with retinal vein occlusion, non-infectious posterior uveitis and diabetic macular edema^[20,21]. To our best knowledge there is a single report by Alten *et al*^[22], where Ozurdex was used in three acute NAION patients in addition to high-dose systemic steroids. Ozurdex was administered five days after the onset of symptoms in one patient and 12 days in the remaining patients. No cataract development was observed in any patient but the follow-up duration was just three months. One patient experienced an elevated intraocular pressure of 23 mmHg, which was controlled easily by the local treatment. Simultaneous systemic, intravitreal steroid administration and the small number of patients should be taken into account when interpreting their results.

A summary of the literature about the intravitreal steroids in acute NAION is summarized in table 1.

VEGF Inhibitors (Bevacizumab, Ranibizumab, Aflibercept)

Vascular endothelial growth factor (VEGF) is one of the most important intraocular cytokine that influences the vascular permeability. Intravitreal anti-VEGF agents were advocated in eyes with acute NAION by some clinicians, as it is believed that anti-VEGF agents may lessen the capillary permeability and thereby the dependent disc edema. On the contrary, several other authors reported some cases who developed acute NAION following the intravitreal injection of a VEGF inhibitor to treat a variety of disease and therefore strongly discouraged the use of anti-VEGF agents in eyes with acute NAION^[23-25]. Mansour *et al*^[25] argued that the potential mechanisms participating in this negative outcome may include the vasoconstrictor effect of the anti-VEGF agents, an acute increase in the intraocular pressure resulting from the injection itself and the exacerbation of systemic hypertension from the stress of the procedure.

In light of this controversy, Miller *et al*^[26] examined the neuroprotective effect of intravitreal ranibizumab in a primate NAION model. As a result, a single intravitreal ranibizumab injection

Table 1 Summary of reports on intravitreal triamcinolone and ozurdex in the treatment of acute naion.

Triamcinolone Acetonide									
Author/Year	Type of Study	Treatment window	Treatment	Number of patients	Functional Outcome (visual acuity and visual field)	Structural Outcome	Age (years)	Follow-up (months)	Adverse events
Jonas <i>et al</i> [16] (2007)	Case series	< 7d	20 mg TA	3	- Case 1: improvement from 0.1 to 0.2 - Case 2: deterioration from 0.5 to 0.2 - Case 3: improvement from 0.16 to 0.2 - no major change in VF in all cases	n.a.	63/66/71	3/3.5/5 month	Ocular hypertension treated with antiglaucomatous drops
Kaderli <i>et al</i> [17] (2007)	Prospective interventional	10 d/10 d/ 12 d/22 d	4 mg TA vs no treatment	4 TA/6 control	TA: Improvement 6,2 ETDRS lines Control: Improvement 1,3 ETDRS lines No improvement in VF defects in both groups	TA: Markedly decrease of disk swelling and leakage at the first week and disappeared by the third week Control: disk swelling at the fourth week	57-67	>9 month	No IOP rise >21 mmHg
Yaman <i>et al</i> [18] (2008)	Case series	4 d/7 d/10 d/10 d	4 mg TA	4	Improvement of VA >3 line: n=2/4 (%50) Improvement of VA <3 line: n=2/4 (%50)	n.a.	44-77	3 month	none
Sohn <i>et al</i> [43] (2009)	Case report	15 d	4 mg TA	1	VA: from 0.05 to 0.4	Significant reduction of disk swelling at first week	65	34	none
Radoi <i>et al</i> [19] (2014)	Retrospective cohort	< 15 d: n = 13 ≥ 15 d: n = 8	4mg TA vs no treatment	21 TA/15 control	Improvement of VA >1 line: 71% TA vs 13% control Improvement of VA >3 line: 29% TA vs 7% control	Significant difference of RNFLT decrement in TA just in 7th day, no difference in 6th month	59-91	(12-61) >6 month	Modest IOP rise under topical brinzolamide
Ozurdex Implant									
Alten <i>et al</i> [22] (2014)	Case series	4d (3-7d)	High dose systemic steroids+intravitreal Dexamethasone implant	3	No gain in VA and VF	Progressive decrease in RNFLT thickness	n.a.	3 month	IOP increase in 1 patient, controlled with topical IOD drops

VA: visual acuity; VF: visual field; n.a.: not available ; IOP: intraocular pressure; TA: triamcinolone acetonide; RNFLT: retinal nerve fiber layer thickness; d:days.

Table 2 Summary of reports on intravitreal anti-vegf agents in the treatment of acute naion.

Author /Year	Nature of the study	Treatment window	Treatment	Number of eyes	Functional Outcome (Visual acuity and visual field)	Structural Outcome	Age (years)	Follow-up (months)
Bennett <i>et al</i> [28] (2007)	Case report	21 d	Intravitreal 1.25 mg bevacizumab	1	VA improvement from counting fingers to 20/100	Rapid resolution of optic disc edema	83	3/3.5/5 month
Pece <i>et al</i> [29] (2010)	Case series	1-2 d	Intravitreal 0.5 mg ranibizumab	3	No improvement in VA and VF in all 3 cases	Resolution of optic disc edema in 1 month	62-81	12 months
Prescott <i>et al</i> [45] (2012)	Retrospective chart review	1-9 d; mean: 5 d	Intravitreal 1.25 mg bevacizumab	5	Stable VA of 20/20 in 4 patients VA Improvement from 20/150 to 20/40 VF: Progression in 3 cases, stable in 1 case, improvement in 1 case	n.a.	40-69	2 weeks - 3 years
Saati <i>et al</i> [30] (2013)	Case series	2-15 d; mean: 7.5 d	Intravitreal 0.5 mg ranibizumab	17	Visual gain in 14/17 eyes (82%) Mean VA Improvement from 1.45 to 0.77 logMAR	RNFLT decrease	41-90	12 month
Samaat <i>et al</i> [31] (2013)	Retrospective chart review	mean: 7.8 d	Intravitreal 0.5 mg ranibizumab	6	VA Improvement in all patients with a mean increase of 2 Snellen lines	RNFLT decrease by an average of 230 µm at 1 month	45-63	>6 month
Rootmann <i>et al</i> [32] (2013)	Non-randomized prospective trial	< 15 d	Intravitreal 1.25 mg bevacizumab vs no treatment	10 bevacizumab /7 control	No significant difference between groups regarding VA, VF	RNFLT decrease in both groups without significant difference	60	1-6 month
Heidart <i>et al</i> [44] (2014)	Prospective case series	< 15 d	Intravitreal 1.25 mg bevacizumab	11	VA improvement in 5 of 11 eyes (45%), noremarkable change in visual field defects	Optic disc edema resolution in 1 week	57	>4weeks
Ayhan <i>et al</i> [33] (2015)	Case report	2 d	Intravitreal 2 mg aflibercept	1	Improvement in VA from 0.1 to 1.0 Marked VF improvement	Progressive decrease in RNFLT	67	3 month

No adverse effects related to the injection was noticed on all of the studies above. d: days; VF: visual field, VA: visual acuity; RNFLT: retinal nerve fiber layer thickness; n.a.: not available.

given immediately after inducing the acute NAION revealed no significant reduction of clinical, electrophysiological or histologic damage. Similar results were reported by Huang *et al.*^[27], in a rat model of anterior ischemic optic neuropathy. They demonstrated that early intravitreal ranibizumab injection did not have a significant protective effect on the function and morphology of the retinal ganglion cells.

There are some studies reporting the effect of anti-VEGF treatments in patients with acute NAION with conflicting results. Bennet and associates^[28] reported their experience in a single case with acute NAION. Early resolution of edema and improved functional outcome was observed following the intravitreal bevacizumab injection performed three weeks after the event. Pece and colleagues^[29] reported three patients with acute NAION of 1-2 days onset, who underwent a single intravitreal ranibizumab injection. In all patients, they noted an early resolution of optic disc swelling a week later. However, the morphological improvement was not accompanied by visual acuity or visual field improvement. In a retrospective case series, we evaluated the effect of a single intravitreal ranibizumab injection in 17 eyes of 16 patients with acute NAION, who experienced a visual loss with duration of 15 days or less (mean: 7.5 days)^[30]. At the end of one year, visual acuity improved in 14 of 17 eyes, stable in one eye and declined in two eyes. Visual fields improved in nine eyes and remained stable in eight eyes. In all eyes the retinal nerve fiber layer thickness decreased dramatically. Samant *et al.*^[31] reported their observations in their retrospective chart analysis of six patients with acute NAION who had a follow-up of six months or more following a single intravitreal ranibizumab injection performed within 15 days of presentation. Visual acuity improved in all eyes with a mean change of two Snellen lines. They noted a rapid resolution of the optic disc edema in four weeks time that was evaluated with SD-OCT. Rootman *et al.*^[32] investigated the efficacy of intravitreal bevacizumab in eyes with acute NAION in a non-randomized prospective trial. They overall enrolled 25 eyes with acute NAION. Seventeen eyes were treated with intravitreal bevacizumab and eight eyes were served as the control eyes without receiving any treatment. Primary outcome measure was the change in mean deviation on Humphrey perimeter and secondary outcome measures were change in visual acuity and optic nerve thickness. Six months later, no difference was found between the injection and control group regarding the change in visual acuity, visual field and retinal nerve fiber thickness. In light of their study, the authors did not recommend intravitreal bevacizumab therapy for the treatment of patients with acute NAION. Recently, we used a single intravitreal aflibercept injection in a 67-year-old male with an unilateral acute NAION one day after the visual loss. Visual acuity improved from 1/10 to 7/10 in the first week. The visual field also improved markedly during the follow-up of three months^[33].

The studies on the administration of anti-VEGF agents are summarized in table 2.

Erythropoietin

Erythropoietin (EPO) is a cytokine hormone that regulates the haematopoiesis as a response to hypoxia and routinely used in the anemia treatment. It is predominantly produced in the fetal liver and adult kidney, but can also be expressed by neurons, glial cells and the cerebrovascular endothelium. It was shown that EPO could act in an angiogenic, neuroprotective and neurotrophic manner in addition to its promoting role in haematopoiesis^[34]. The efficacy of EPO was evaluated in patients with optic neuritis due to its neuroprotective properties by Sühs and colleagues^[35]. In a double-blind, placebo-

controlled trial, they treated 20 optic neuritis patients with systemic EPO and compared them with 17 placebo-treated patients. Significant morphological differences between the two groups were observed in the study and retinal nerve fiber layer thinning was found to be less in the EPO treated group. Furthermore, the retrobulbar optic nerve diameter was more thicker in the EPO group. Visual evoked potential (VEP) latencies were shorter in the EPO-treated patients at the week 16, and visual functions were also improved after the EPO treatment. Modarres *et al.*^[36] treated 31 patients with acute NAION intravitreally with EPO within 30 days of symptom onset (mean, 11 days). On the sixth postoperative month, visual acuity improved at least three Snellen lines in 17 of 31 patients (55%) but perimetric findings did not significantly differ from the baseline. No ocular or systemic side effect was reported. The authors argued that EPO could be a safe and effective intravitreal agent in the treatment of acute NAION and the effect of intravitreal EPO might last as long as a month.

Caspase-2 Inhibitor (QPI-1007)

QPI-1007 is a chemically modified small interfering RNA (siRNA) designed to act as a neuro protective agent via a temporary inhibition of the caspase-2 protein expression. It was developed for the treatment of optic neuropathies including the glaucomatous optic nerve damage and acute NAION. Preclinical studies investigated the intravitreal and intravenous administrations and no major ocular or systemic toxicity was detected^[37]. In a phase 1 trial, Katz *et al.*^[38] administered this compound intravitreally in 30 patients with acute NAION within 30 days of symptom onset. They observed a visual acuity improvement of at least three Snellen lines in half of the patients followed up for six months.

Fasudil

Inhibition of the Rho/Rho kinase pathway has been shown to be effective in the management of ischemia-induced pathological conditions via the upregulation of nitric oxide and downregulation of microglia activity^[39]. Specifically, a rodent model of ischemic optic neuropathy demonstrated an increased RhoA activation^[40]. Fasudil is a Rho-kinase inhibitor targeting the ATP-dependent kinase domain of ROCK (Rho-associated coiled-coil-containing protein kinase). Sugiyama *et al.*^[41] showed that topical or intravenous administration of fasudil might have a positive effect on optic nerve head perfusion. In a recent interventional case series, Sanjari *et al.*^[42] investigated the effect of intravitreal fasudil in 13 eyes with acute NAION within 14 days of symptom onset. During the follow-up of three months, optic disc edema gradually decreased and the best-corrected visual acuity improved from 1,69 to 0,93 log MAR. Visual field improved slightly, with a modest change in mean deviation from -24,6 to -20,5 dB. None of the patients experienced any ocular or systemic adverse event.

CONCLUSIONS

In view of the above mentioned case reports and small, heterogeneous, uncontrolled studies it is not possible to reach a valid conclusion about the effect of intravitreal pharmacotherapy in acute NAION. Though scientifically unproven, various intravitreally administered agents seem to lessen the optic disc edema relatively quickly. In contrast, functional results are less convincing. The current data also do not enable us to compare the various administered intravitreal agents. Due to scarcity of adverse effects observed with anti-VEGF agents, they may be preferred over the intravitreal steroids if an intravitreal therapy is considered for the treatment of acute NAION. It

is evident that only randomized controlled trials involving a sufficient number of patients can yield an adequate information to ascertain the place of intravitreal pharmacotherapy in eyes with acute NAION.

REFERENCES

- 1 Arnold AC. The 14th Hoyt Lecture: Ischemic optic neuropathy: The evolving profile, 1966-2015. *J Neuroophthalmol* 2016; **36**: 208-215. [PMID: 27176556]; [DOI: 10.1097/WNO.0000000000000395]
- 2 Xu L, Wang Y, Jonas JB. Incidence of nonarteritic anterior ischemic optic neuropathy in adult Chinese: the Beijing Eye Study. *Eur J Ophthalmol* 2007; **17**: 459-460. [PMID: 17534837]
- 3 Hattenhauer MG, Leavitt JA, Hodge DO, Grill R, Gray DT. Incidence of nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1997; **123**: 103-107. [PMID: 9186104]; [DOI: [http://dx.doi.org/10.1016/S0002-9394\(14\)70999-7](http://dx.doi.org/10.1016/S0002-9394(14)70999-7)]
- 4 Rosčić V, Bojić L, Marović T. The incidence of nonarteritic ischemic optic neuropathy in the Split-Dalmatia County. *Acta Med Croatica* 2009; **63**: 169-172. [PMID:19580225]
- 5 Hayreh SS, Podhajsky P, Zimmerman MB. Role of nocturnal arterial hypotension in optic nerve head ischemic disorders. *Ophthalmologica* 1999; **213**: 76-96. [PMID: 9885384]; [DOI:10.1159/000027399]
- 6 Arnold AC. Pathogenesis of nonarteritic anterior ischemic optic neuropathy. *J Neuro-Ophthalmol* 2003; **23**: 157-163. [PMID: 12782932]
- 7 Beck RW, Servais GE, Hayreh SS. Anterior ischemic optic neuropathy. IX. Cup-to-disc ratio and its role in pathogenesis. *Ophthalmology* 1987; **94**: 1503-1508. [PMID: 3684223]; [DOI: [http://dx.doi.org/10.1016/S0161-6420\(87\)33263-4](http://dx.doi.org/10.1016/S0161-6420(87)33263-4)]
- 8 Burde RM. Optic disk risk factors for nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1993; **116**: 759-764. [PMID: 8250081]; [DOI: [http://dx.doi.org/10.1016/S0002-9394\(14\)73478-6](http://dx.doi.org/10.1016/S0002-9394(14)73478-6)]
- 9 Miller NR, Arnold AC. Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. *Eye* 2015; **29**: 65-79. [PMID: 24993324]; [DOI: 10.1038/eye.2014.144]
- 10 Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for NAION is not effective and may be harmful. *JAMA* 1995; **273**: 625-632. [PMID: 7844872]; [DOI:10.1001/jama.1995.03520320035038]
- 11 Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: natural history of visual outcome. *Ophthalmology* 2008; **115**: 298-305. [PMID: 17698200]; [DOI:10.1016/j.ophtha.2007.05.027]
- 12 Zhang C, Guo Y, Miller NR, Bernstein SL. Optic nerve infarction and post-ischemic inflammation in the rodent model of anterior ischemic optic neuropathy (raION). *Brain Res* 2009; **1264**: 67-75. [PMID: 19401181]; [DOI: 10.1016/j.brainres.2008.12.075]
- 13 Salgado C, Vilson F, Miller NR, Bernstein SL. Cellular inflammation in nonarteritic anterior ischemic optic neuropathy and its primate model. *Arch Ophthalmol* 2011; **129**: 1583-1591. [PMID: 22159678]; [DOI: 10.1001/archophthalmol.2011.351]
- 14 Huang TL, Huang SP, Chang CH, Lin KH, Chang SW, Tsai RK. Protective effects of systemic treatment with methylprednisolone in a rodent model of non-arteritic anterior ischemic optic neuropathy (raION). *Exp Eye Res* 2015; **131**: 69-76. [PMID: 25543054]; [DOI: 10.1016/j.exer.2014.12.014]
- 15 Hayreh SS, Zimmerman MB. Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. *Graefes Arch Clin Exp Ophthalmol* 2008; **246**: 1029-1046. [PMID: 18404273]; [DOI: 10.1007/s00417-008-0805-8]
- 16 Jonas JB, Spandau UH, Harder B, Sauder G. Intravitreal triamcinolone acetonide for treatment of acute nonarteritic anterior ischemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2007; **245**: 749-750. [PMID: 16673138]; [DOI: 10.1007/s00417-006-0332-4]
- 17 Kaderli B, Avci R, Yucel A, Guler K, Gelisken O. Intravitreal triamcinolone improves recovery of visual acuity in nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol* 2007; **27**: 164-168. [PMID: 17895814]; [DOI: 10.1097/WNO.0b013e31814a5a9a]
- 18 Yaman A, Selver OB, Saatci AO, Soylev MF. Intravitreal triamcinolone acetonide injection for acute non-arteritic anterior ischaemic optic neuropathy. *Clin Exp Optom* 2008; **91**: 561-564. [PMID: 19570152]; [DOI: 10.1111/j.1444-0938.2009.00366.x]
- 19 Radoi C, Garcia T, Brugniart C, Ducasse A, Arndt C. Intravitreal triamcinolone injections in non-arteritic anterior ischemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2014; **252**: 339-345. [PMID: 24178807]; [DOI: 10.1007/s00417-013-2499-9]
- 20 Haller JA, Bandello F, Belfort R Jr *et al.* Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. *Ophthalmology* 2011; **118**: 2453-2460. [PMID: 21764136]; [DOI: 10.1016/j.ophtha.2011.05.014]
- 21 Boyer DS, Yoon YH, Belfort R Jr *et al.* Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014; **121**: 1904-1914. [PMID: 24907062]; [DOI: 10.1016/j.ophtha.2014.04.024]
- 22 Alten F, Clemens CR, Heiduschka P, Eter N. Intravitreal dexamethasone implant [Ozurdex] for the treatment of nonarteritic ischaemic optic neuropathy. *Doc Ophthalmol* 2014; **129**: 203-207. [PMID: 25274269]; [DOI: 10.1007/s10633-014-9461-y]
- 23 Ganssauge M, Wilhelm H, Bartz-Schmidt KU, Aisenbrey S. Nonarteritic anterior ischemic optic neuropathy (NA-AION) after intravitreal injection of bevacizumab (Avastin) for treatment of angoid streaks in pseudoxanthoma elasticum. *Graefes Arch Clin Exp Ophthalmol* 2009; **247**: 1707-1710. [PMID: 19916212]; [DOI:10.1007/s00417-009-1184-5]
- 24 Hosseini H, Razeghinejad MR. Anterior ischemic optic neuropathy after intravitreal injection of bevacizumab. *J Neuroophthalmol* 2009; **29**: 160-161. [PMID: 19491650]; [DOI: 10.1097/WNO.0b013e3181a58fd1]
- 25 Mansour AM, Schwartz SG, Gregori NZ *et al.* Insight into 8 patients with nonarteritic anterior ischemic optic neuropathy following anti-VEGF injections. *J Neuroophthalmol* 2012; **32**: 193. [PMID: 22549561]; [DOI: 10.1097/WNO.0b013e3182569e7b]
- 26 Miller NR, Johnson MA, Nolan T, Guo Y, Bernstein SL. A single intravitreal injection of ranibizumab provides no neuroprotection in a nonhuman primate model of moderate-to-severe nonarteritic anterior ischemic optic neuropathy. *Invest Ophthalmol Vis Sci* 2015; **56**: 7679-7686. [PMID: 26624498]; [DOI: 10.1167/iovs.15-18015]
- 27 Huang TL, Chang CH, Chang SW, Lin KH, Tsai RK. Efficacy of intravitreal injections of antivascular endothelial growth factor agents in a rat model of anterior ischemic optic neuropathy. *Invest Ophthalmol Vis Sci* 2015; **56**: 2290-2296. [PMID: 25758818]; [DOI: 10.1167/iovs.14-15999]
- 28 Bennett JL, Thomas S, Olson JL, Mandava N. Treatment of nonarteritic anterior ischemic optic neuropathy with intravitreal bevacizumab. *J Neuroophthalmol* 2007; **27**: 238-240. [PMID: 17895825]; [DOI: 10.1097/WNO.0b013e31814b273d]
- 29 Pece A, Querques G, Quinto A, Isola V. Intravitreal ranibizumab injection for nonarteritic ischemic optic neuropathy. *J Ocul Pharmacol Ther* 2010; **26**: 523-527. [PMID: 20874667]; [DOI: 10.1089/jop.2010.0053]
- 30 Saatci AO, Taskin O, Selver OB, Yaman A, Bajin MS. Efficacy of intravitreal ranibizumab injection in acute nonarteritic ischemic optic neuropathy: a long-term follow up. *Open Ophthalmology Journal*. 2013; **7**: 58-62. [PMID: 24133556]; [DOI: 10.2174/1874364101307010058]

- 31 Samant PM, Samant HP, Saraiya KA. Single intravitreal ranibizumab injection in eyes with acute non-arteritic anterior ischemic optic neuropathy. *Journal of Clinical Ophthalmology and Research* 2013; **1**: 27-28. [PMID: 21255078]; [DOI: 10.1111/j.1444-0938.2010.00570.x]
- 32 Rootman DB, Gill HS, Margolin EA. Intravitreal bevacizumab for the treatment of nonarteritic anterior ischemic optic neuropathy: a prospective trial. *Eye* 2013; **27**: 538-544. [PMID: 23370417]; [DOI: 10.1038/eye.2012.296]
- 33 Ayhan Z, Kocaoglu G, Yaman A, Bajin MS, Saatci AO. Single intravitreal aflibercept injection for unilateral acute nonarteritic ischemic optic neuropathy. *Case Rep Ophthalmol Med* 2015; **2015**: 783241. [PMID: 25632361]; [DOI: 10.1155/2015/783241]
- 34 Genc S, Koroglu TF, Genc K. Erythropoietin and the nervous system. *Brain Res* 2004; **1000**: 19-31. [PMID: 15053948]; [DOI: 10.1016/j.brainres.2003.12.037]
- 35 Sühs KW, Hein K, Sattler MB. A randomized, double-blind, phase 2 study of erythropoietin in optic neuritis. *Ann Neurol* 2012; **72**: 199-210. [PMID: 22926853]; [DOI: 10.1002/ana.23573]
- 36 Modarres M, Falavarjani KG, Nazari H *et al.* Intravitreal erythropoietin injection for the treatment of non-arteritic anterior ischaemic optic neuropathy. *Br J Ophthalmol* 2011; **95**: 992-995. [PMID: 21131378]; [DOI: 10.1136/bjo.2010.191627]
- 37 Solano EC, Kornbrust DJ, Beaudry A, Foy JW, Schneider DJ, Thompson JD. Toxicological and pharmacokinetic properties of QPI-1007, a chemically modified synthetic siRNA targeting caspase 2 mRNA, following intravitreal injection. *Nucleic Acid Ther* 2014; **24**: 258-266. [PMID: 25054518]; [DOI: 10.1089/nat.2014.0489]
- 38 Katz DM, Trobe JD. Is there treatment for nonarteritic anterior ischemic optic neuropathy. *Curr Opin Ophthalmol* 2015; **26**: 458-463. [PMID: 26367094]; [DOI: 10.1097/ICU.0000000000000199]
- 39 Bye N, Christie KJ, Turbic A, Basrai HS, Turnley AM. Rho kinase inhibition following traumatic brain injury in mice promotes functional improvement and acute neuron survival but has little effect on neurogenesis, glial responses or neuroinflammation. *Exp Neurol* 2016; **279**: 86-95. [PMID: 26896832]; [DOI: 10.1016/j.expneurol.2016.02.012]
- 40 Fard MA, Ebrahimi KB, Miller NR. RhoA activity and post-ischemic inflammation in an experimental model of adult rodent anterior ischemic optic neuropathy. *Brain Res* 2013; **1534**: 76-86. [PMID: 23973747]; [DOI: 10.1016/j.brainres.2013.07.053]
- 41 Sugiyama T, Shibata M, Kajjura S *et al.* Effects of fasudil, a Rho-Associated Protein Kinase Inhibitor, on optic nerve head blood flow in rabbits. *Invest Ophthalmol Vis Sci* 2011; **52**: 64-69. [PMID: 20720232]; [DOI: 10.1167/iovs.10-5265]
- 42 Sanjari N, Pakravan M, Nourinia R *et al.* Intravitreal Injection of a Rho-kinase inhibitor (Fasudil) for recent-onset nonarteritic anterior ischemic optic neuropathy. *J Clin Pharmacol* 2016; **56**: 749-753. [PMID: 26444290]; [DOI: 10.1002/jcph.655]
- 43 Sohn BJ, Chun BY, Kwon JY. The effect of an intravitreal triamcinolone acetonide injection for acute nonarteritic anterior ischemic optic neuropathy. *Korean J Ophthalmol* 2009; **23**: 59-61. [PMID: 19337484]; [DOI: 10.3341/kjo.2009.23.1.59]
- 44 Heidari E, Niyousha MR, Heidari R, Rahimi-Aradabili B, Adl FH, Bazzazi N. Intravitreal bevacizumab in nonarteritic anterior ischemic optic neuropathy. *Advances in Bioscience & Clinical Medicine* 2015; **2**: 23-26. [DOI: 10.7575/aiaac.abcm.v.2n.1p.18]
- 45 Prescott CR, Sklar CA, Lesser RL, Adelman RA. Is intravitreal bevacizumab an effective treatment option for nonarteritic anterior ischemic optic neuropathy? *J Neuroophthalmol* 2012; **32**: 51-53. [PMID: 22269947]; [DOI: 10.1097/WNO.0b013e318240596e]

Peer reviewer: Xiaogang Wang