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Intravitreal triamcinolone injections in non-arteritic anterior ischemic optic neuropathy

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Abstract
Background In non-arteritic anterior ischemic optic neuropathy (NA-AION), no treatments have demonstrated to be effective in recovering visual loss in randomized clinical trials. Oral steroids have been evaluated, and small series of intravitreal triamcinolone acetonide (IVTA) injection in NA-AION have been reported. The purpose of our study was to report the visual outcome and morphological changes in response to a single IVTA injection as a treatment for patients with NA-AION.
Patients and methods The charts of 36 patients with visual symptoms and optic disc swelling caused by NA-AION were evaluated. Twenty-one patients had received 4 mg IVTA and were compared with 15 non-treated patients. Visual acuity (VA), retinal nerve fiber layer thickness and static visual field were evaluated after 6 months.
Results VA improvement at 6 months is statistically better in the treated group than in the non-treated group ($p = 0.0035$). In the treated group, there was a significant inverse correlation between the delay of the injection and the visual acuity achieved at 6 months ($p < 0.0083$**, $r = -0.56$). A significant improvement of the visual field was noted in the injected group when compared with the non-treated group at 6 months ($p < 0.0028$).
Discussion In this retrospective study, patients receiving IVTA in the acute phase of NA-AION have better improvement of VA and visual field during the follow-up period of 6 months. However, only a large randomized controlled trial may enable to evaluate the benefits of IVTA Injections on visual outcome in NA-AION.

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Introduction

Non-arteritic ischemic optic neuropathy (NA-AION) is the most common cause of acute optic nerve ischemic disease in a middle-aged and elderly population, and often results in severe visual loss [1, 2]. Clinically, NA-AION is characterized by sudden and painless loss of vision associated with pallid swelling of the optic disc. Pathogenetically, NA-AION is caused by hypoperfusion of the optic nerve head circulation by transient occlusion of capillaries of the posterior ciliary arteries, producing ischemia of the optic nerve head [3].

It is often associated with cardio-vascular predisposing risk factors: arterial hypertension, diabetes mellitus, hyperlipidemia, arteriosclerosis, nocturnal hypotension, and sleep apnea [4–7], and also with anatomical factors such as small crowded discs or optic disc druses [8].

It clinically results in ischemic edema of part or the entire disc, which appears white and swollen.

The management of NA-AION is actually controversial. Various treatments have been suggested in order to improve vision in patients with acute NA-AION (intravitreal anti-VEGF injections, antiaggregants, and optic nerve decompression [9–13]) but no treatment recommendation is generally admitted.

Micro inflammatory mechanisms seem to be involved in disc swelling and in the auto-maintained phenomenon of ischemia. Prolonged ischemia of the disc leads to axonal loss within the optic nerve head. This leads to optic atrophy, which appears several months after the acute edema.

In order to limit the inflammatory process and to reduce the vicious circle of ischemia, the use of steroids appears to be the most logical treatment.

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Systemic high-dose steroid treatment in the acute phase of NA-AION is the only treatment which showed encouraging results in a large cohort of 312 patients treated with decreasing oral steroids [14].

Intravitreally administered steroids compared with systemic treatment potentially avoid harmful side-effects, especially in the fragile background of patients with NA-AION who often have cardiovascular and metabolic disturbances.

However, only a few pilot studies have reported intravitreal use of steroids in this disease.

The purpose of the present controlled study was to further evaluate the potential benefits of an intravitreal injection of steroids in the initial phase of NA-AION.

Patients and methods

The charts of consecutive patients presenting with isolated optic disc edema characteristic of recent NA-AION (history of visual acuity loss of less than 1 month) at Reims University hospital between February 2009 and November 2012 and completing a minimum follow-up of at least 6 months were reviewed. Both injected and non-injected patients were considered for analysis: injected patients were cases, they were compared to the untreated group.

Exclusion criteria

On the base of the chart analysis, patients with history or clinical symptoms of arteritic AION or elevated C-reactive protein and erythrocyte sedimentation rate levels were excluded. If a temporal artery biopsy was performed, normality was required, otherwise the patient was excluded. Other exclusion criteria were onset of symptoms for more than 1 month, other associated ocular diseases that could be responsible for visual loss (such as glaucoma, macular disorders, diabetic retinopathy, lens opacities), previous intravitreal or systemic steroid treatments. The results of best-corrected visual acuity, static perimetry, and time-domain optical coherence tomography were noted.

Visual acuity evaluation

Best-corrected visual acuity was evaluated with an EDTRS-based chart and a French near vision test (Parinaud). For both far and near vision, a LogMAR equivalent was calculated. Visual acuity rating (VAR) [15, 16] was used to compare the visual acuity shift between the first visit and the different follow-up visits. VAR is an inversion of the LogMAR scale, based on the formula VAR=100 – 50× LogMAR. This scale avoids decimal values, higher values indicating better VA. Thus the visual acuity shift (gain or loss) are expressed in VAR letters or lines (1 line= 0.1LogMAR=5 VAR letters).

Visual field evaluation

FAST 30 static perimetry (Ophthalmic Monitor, Metrovision, France) was performed at onset, at 1 month, and 6 months after presentation. Corrected mean deviation was analyzed to evaluate visual field evolution. The mean deviation shift between 1 month and 6 months and at baseline was calculated.

Retinal nerve fiber thickness

Time-domain optical coherence tomography (Stratus, Carl Zeiss Meditec, Dublin, CA, USA) of the retinal nerve fiber layer (RNFL) was generally performed at presentation and 7 days, 1 month, and 6 months. The measures were considered only if the quality of the measure was good (>6). The decrement of optic disc edema was evaluated by comparing the initial mean RNFL thickness with the recordings performed at 7 days, 1 months, 3 months, and 6 months.

Intraocular injection protocol

Informed consent had been obtained from all patients prior to injection. In the acute phase of NA-AION, once the diagnosis was established, a single intravitreal injection of 4 mg/0.1 ml triamcinolone acetonide (IVTA) was performed. Triamcinolone was filtered in order to eliminate the excipients in the commercial available solution. A systematic treatment with brinzolamide was administrated in all cases after the injection, in order to prevent ocular hypertension caused by triamcinolone [17, 18].

Statistical methods

For descriptive analysis, quantitative variables were expressed as mean values with standard deviation; qualitative variables were expressed as percentage. Mann–Whitney tests were used to compare quantitative variables. A Chi2 test was used to compare qualitative variables. Results are considered as statistically significant if $p< 0.05$ %.

Results

Demographic characteristics

The charts of 36 patients were included; 21 received IVTA of whom 13 were injected before 15 days and 8 after 15 days. Fifteen patients did not receive treatment. The patients are all Caucasians, aged from 59 to 91 years (Table 1).

Table 1 Demographic characteristics, IVTA, delay since onset and EDTRS chart logMAR visual acuity (VA) and logMAR near visual acuity (NVA)

	Injection	Age	Delay(days)	VA t=0	NVA t=0	VA t=30	NVA t=30	VA t=90	NVA t=90	VA t=180	NVAt=180
Patient1	Y	75	2	0.1	0.1	0	0	0	0	0	0
Patient2	Y	73	3	0.7	0.4	0.2	0.1	0.2	0.1	0.2	0
Patient3	Y	69	4	1.7	1.3	0.3	0.4	0.3	0.3	0.2	0.3
Patient4	Y	60	4	1.7	1.7	1	1	0.8	1	0.8	1
Patient5	Y	64	5	1.7	1.2	0.6	0.7	0.5	0.6	0.4	0.5
Patient6	Y	61	5	1.7	1.7	1	0.9	0.7	0.7	0.7	0.7
Patient7	Y	77	6	1.1	1.1	1	1	1	1	1	1
Patient8	Y	65	7	0.4	0.6	0.3	0.4	0.3	0.4	0.3	0.3
Patient9	Y	61	8	1.1	1.1	1	0.9	0.7	0.2	0.6	0.25
Patient10	Y	73	8	0.4	0.7	0.2	0.1	0.2	0.1	0.2	0.1
Patient11	Y	83	10	0.3	0.2	0.3	0.1	0.3	0.1	0.3	0.1
Patient12	Y	62	10	0.5	0.8	0.3	0.2	0.3	0.2	0.3	0.2
Patient13	Y	55	14	1.2	1.2	1.1	1.1	1.1	1.1	1.1	1.1
	means injected<15 days			0.97	0.93	0.56	0.53	0.49	0.45	0.47	0.43
Patient14	Y	71	15	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Patient15	Y	48	16	1.7	1.9	1.7	1.9	1.7	1.9	1.7	1.9
Patient16	Y	85	16	2	2	1.8	1.8	1.8	1.8	1.8	1.8
Patient17	Y	59	17	0.4	0.3	0.2	0.1	0.2	0.1	0.2	0.1
Patient18	Y	89	21	1.5	1.5	1.2	1.2	1.2	1.2	1.2	1.2
Patient19	Y	56	21	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Patient20	Y	59	30	0.3	0.4	0.3	0.4	0.3	0.4	0.4	0.4
Patient21	Y	77	30	0.8	0.8	1	1	1	0.8	0.8	0.8
	means injected>15 days			1.26	1.29	1.2	1.22	1.2	1.2	1.19	1.2
	means injected			1.08	1.07	0.81	0.80	0.769	0.74	0.75	0.73
Patient1	N	73	4	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2
Patient2	N	65	4	1	0.1	0.1	0	0.1	0	0.1	0
Patient3	N	73	5	0.3	0.3	0.4	0.4	0.4	0.4	0.4	0.4
Patient4	N	72	7	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Patient5	N	85	8	0.6	0.5	1.7	1.7	1.7	1.7	1.7	1.7
Patient6	N	79	8	1	1	1	1	1	1	1	1
Patient7	N	68	10	0.2	0.1	0.3	0.2	0.4	0.2	0.4	0.3
Patient8	N	71	10	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Patient9	N	69	15	0	0	0.1	0.2	0.1	0.2	0.1	0.2
Patient10	N	77	15	0.3	0.1	0.4	0.3	0.4	0.3	0.4	0.3
Patient11	N	91	15	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Patient12	N	57	21	0.5	0.5	0.7	0.5	0.5	0.5	0.4	0.5
Patient13	N	64	30	1	1	0.3	0.2	0.2	0.2	0.1	0.1
Patient14	N	65	30	0	0	0.1	0.1	0.1	0	0.1	0
Patient 15	N	84	30	2	2	2	2	2	2	2	2
	means non-injected			0.8	0.72	0.81	0.78	0.8	0.77	0.79	0.77

(Y = yes N = no)

Visual acuity

There was no statistical difference in terms of baseline visual acuity between the group of patients injected and the patients in the non injected group of patients (p =0.3414). In addition, the baseline visual acuity was not significantly different between the subgroup of patients injected before 15 days and the non-injected group of patients presenting before 15 days (p =0.5699). Similarly, the baseline acuity between the group of patients injected after 15 days end the non-injected group presenting after 15 days was not significantly different (p =0.62).

Table 2 Comparing visual acuity change (gain or loss) of more than 1 line between the injected and the non-injected group: a statistical significant difference between the two groups (Chi-square test, $p=0.0009$)

	Injected, $n=21$	Non injected, $n=15$
Improved VA>1 line	15 (71 %)	2 (13 %)
Stable	5 (24 %)	6 (40 %)
Worsened VA<1 line	1 (5 %)	7 (47 %)

At the end of the study period (6 months), a higher proportion of patients with an improved VA of more than 1 line (> 5 VAR letters) were observed in the injected group [15 patients (71 %)] versus the non-treated group [two patients (13 %)], which was statistically significant ($p=0.0009$) (Table 2).

At 6 months, a higher proportion of patients also had a VA improvement of more than 3 lines (>15 VAR letters) in the treated group [six patients [29 %]) versus in the not-treated group [one patient (7 %)]; however, this difference did not reach statistical significance ($p=0.0803$) (Table 3).

In the subgroup analysis of early injection versus early presentation, the percentage of patients gaining more than 3 lines was not significantly better in the early injected group than in the non-injected group ($p=0.1153$). However, there was a significantly higher percentage of patients gaining more than 1 line in the early injected group than in the non-injected group with early presentation ($p=0.0296$) (Table 4).

In the subgroup analysis of late injection versus late presentation: the percentage of patients gaining either more than 3 lines or more than one line was not significantly different in the injected group compared with the non-injected group (both $p=0.2367$) (Table 5).

Nevertheless, the delay before injection seems to be an important factor in VA improvement. The average VAR improved in all groups during the follow up period. VAR improvement at 6 months is statistically better in the treated group than the non-treated group ($p=0.0035$), which confirms the previous data. However, interestingly in a subgroup analysis, only the patients treated before 15 days had a significantly higher VAR shift compared with the untreated group ($p=0.0007$ %*) (Table 6).

Table 3 Comparing visual acuity change (gain or loss) of more than 3 lines between the injected group and the non-injected group: no statistical significant difference between the two groups (Chi-square test $p=0.0803$)

	Injected, $n=21$	Non injected, $n=15$
Improved VA>3 lines	6 (29 %)	1 (7 %)
Stable	15 (71 %)	12 (80 %)
Worsened VA<3 lines	0	2 (13 %)

Table 4 Comparing visual acuity change (gain or loss) of more than 1 line and more than 3 lines between the group injected before 15 days, and the non-treated group with symptoms<15 days: statistically significant difference ($p=0.0296$) for more than 1 line, non statistically significant for more than 3 lines ($p=0.1153$)

	Injected before 15 days, $n=13$	Non injected, early presentation, $n=8$
Improved VA>1 line	12 (92 %)	4 (50 %
Stable	1 (8 %)	4 (50 %)
Worsened VA<1 line	0	0

Regression analysis also confirmed the importance of the time frame of the intraocular injection, an inverse correlation between delay of injection and VAR improvement was demonstrated ($p< 0.0083$*; $r=-0.56$).

Visual field (Table 7)

An improvement of visual field (decrement of the mean deviation) was noted in the treated group while in the not treated group, visual field remains stable or deteriorates. The difference between groups is significant at 1 month ($p=0.007$) and 6 months ($p=0.0028$). While it is statistically significant, the visual field improvement does not seem clinically important.

Retinal nerve fiber layer (Table 8)

A significant difference of decrement of RNFL thickness was noted between the two groups at 7 days from onset ($p=0.0017$*). But there was no significant difference of the RNFL thickness shift at 1, 3, and 6 months between the two groups.

Intraocular pressure (Table 9)

Mean intraocular pressure was significantly higher at 3 months in the treated group versus the non-treated group; there was no statistically significant difference at baseline, 7 days, 1 month, and 6 months.

The intraocular pressure shift from baseline was significantly higher in the treated group throughout the follow up (7 days, 1,

Table 5 Comparing visual acuity change (gain or loss) of more than 1 line and more than 3 lines between the group injected after 15 days and the not treated group with symptoms>15 days: non statistically significant for both 1 line and 3 lines (both $p=0.2367$)

	Injected before 15 days, $n=13$	Non injected, early presentation, $n=8$
Improved VA>3 lines	5 (38.5 %)	0
Stable	8 (61.5 %)	6 (75 %)
Worsened VA<3 lines	0	2 (25 %)

Table 6 Comparing the mean variation of the visual acuity rate (VAR) at 1 month (M1), 3 months (M3) and 6 months (M6) between the injected group and the non-treated group, the early injection group (<15 days) and the non-treated group, the late injection group (>15 days) and the non-treated group (* = statistically significant). Visual recovery is significantly better in the injected group than in the non treated group and especially in patients treated before 15 days, whereas there seems to be no clear benefit of an injection after 15 days from onset

	Injected after 15 days, $n=8$	Non injected, late presentation, $n=7$
Improved VA>1 lines	3 (37.5 %)	2 (28.5 %)
Stable	4 (50 %)	2 (28.5 %)
Worsened VA<1 lines	1 (12.5 %)	3 (43 %)
Improved VA>3 lines	1 (13 %)	1 (14 %)
Stable	7 (87 %)	6 (86 %)
Worsened VA<3 lines	0	0

3, and 6 months)when applying a Mann–Whitney test (respectively, $p=0.0115$, $p=0.0035$, $p=0.0002$, $p=0.0013$).

Ocular pressure remains within normal range (10–21 mm Hg) during the whole study period in all patients but one. This patient presented with 25 mm Hg at 3 months after discontinuing brinzolamide treatment, which was resolved with reintroduction of brinzolamide.

Discussion

In this retrospective non-randomized controlled study, patients treated with IVTA in the initial phase of NA-AION have a significantly better visual outcome in terms of VA and visual field at 1, 3, and 6 months compared with non-treated patients. The duration of evolution before injection seems to be an important factor in VA improvement; after 6 months of follow-up, only patients injected before 15 days significantly improved visual acuity compared with the non-treated group.

Table 7 Visual field evolution: the variation of the mean deviation (MD) from onset at 1 month (M1) and 6 months (M6) was significantly different between the injected and the non-injected group (*= statistically significant). A visual field recovery was noted at 1 month and 6 months of the initial visit in the group of injected patients in comparison with the non-injected patients

	Injected, $n=21$	P	Non injected, $n=15$
Mean variation of VAR M1	13.81	0.0034*	0.33
Mean variation of VAR M3	16.9	0.0012*	0.33
Mean variation of VAR M6	16.9	0.0035*	0.67
	Injected<15 days, $n=13$		
Mean variation of VAR M1	20.38	0.0007*	0.33
Mean variation of VAR M3	23.85	0.0006*	0.33
Mean variation of VAR M6	25	0.0007*	0.67
	Injected>15 days, $n=8$		
Mean variation of VAR M1	3.13	0.249	0.33
Mean variation of VAR M3	5.63	0.074	0.33
Mean variation of VAR M6	3.75	0.258	0.67

Table 8 RNFL thickness variation from onset. Comparison of treated and not treated groups (*= statistically significant). The RNFL thickness reduction was more important at 7 days after presentation in the treated patients

	Injected, $n=13$	Non injected, $n=7$	P
Variation of MD M1	−1.33 (±1.9)	1.77 (±2.5)	0.007*
Variation of MD M6	−1.76 (±2.5)	0.53 (±1.2)	0.0028*
	Injected, $n=20$		
Mean RNFL Variation Day7	−63 (±46.1)	−16 (±21.8)	0.0017*
Mean RNFL Variation M1	−90 (±63)	−134 (±65.3)	0.11
Mean RNFL Variation M3	−153 (±65.5)	−94 (±73.7)	0.067
Mean RNFL Variation M6	−154 (±62.2)	−120 (±69)	0.36

The evaluation of natural history [11, 19, 20] had shown that mild VA improvement occurs naturally in NA-AION, but it was hypothesized that this might be partially due to eccentric fixation. An improvement of the visual field has also been noted in the present series at 1 month and 6 months. Thus, improvement of both VA and visual field could be interpreted as a global improvement of visual function.

A few studies evaluated IVTA Injections in NA-AION and found contradictory results [21–25]. Jonas [21] treated three patients with triamcinolone IVT, and reported one improvement of both VA and visual field, one patient remaining stable and one having worse VA and no visual field change.

Yamann [22] reported a benefit of triamcinolone IVT when administered less than 10 days after the first symptoms in four patients with NA-AION, with improvement of both VA and visual field.

Kardeli [23] noted VA improvement in four patients who received triamcinolone IVT without visual field improvement. Another case report on one patient injected 4 days after visual loss mentioned VA improvement [24].

Hayreh noted VA and visual field loss in some patients treated with IVTA [25]. No VA loss greater than 3 lines or visual field loss was found in the treated group of the present series, thus intravitreal triamcinolone IVT appeared to engender at least stability of visual function.

In the present study, the encouraging visual results in patients treated with IVTA were associated with a faster initial resolution of optic disc swelling, which was noted immediately after the injection, as RNFL thickness was significantly lower in the injected group at 7 days compared with the non-injected

Table 9 Mean IOP measured at each examination in treated and not treated groups (minimal = min and maximal = max IOP). The difference between the two groups only reached statistical significance at 3 months from onset (*= statistically significant). Note the peak of 25 mm Hg at 3 months after IVTA corresponding to the only patient with an IOP above 21 mm Hg

Mean IOP	Day 0	Day 7	M1	M3	M6
Treated, $n=21$	14.1 (10–19)	15.95 (10–20)	16.85 (11–21)	17.95 (13–25)	16.35 (13–21)
Not treated, $n=15$	15.1 (12–20)	14.7 (11–17)	14.77 (13–17)	15.1 (12–18)	14.8 (12–19)
P	0.3201	0.1178	0.1178	0.0056*	0.0883

patients, which was not found at 1, 3, or 6 months of onset. As with oral steroid treatment [26] in patients who received IVTA, the resolution of optic disc swelling appears to be faster.

This could account for the significant visual improvement observed in the group of patients who received IVTA linked to pathophysiological mechanisms of NA AAION.

In the initial phase of NA-AION, the hypoperfusion of short posterior ciliary arteries results in primary ischemia of optic nerve head, which is a multifactorial process often related to vascular risk factors and local factors such as a crowded disc. Ischemia of optic nerve axons results in axoplasmic flow stasis, and leads to swelling. Capillaries are compressed by swollen nerve fibers, which lead to secondary ischemia and a self-sustained process [14, 27–34]. Steroids could possibly act by decreasing inflammation among optic nerve axons and decompressing optic nerve head vascularization. The role of the micro-inflammatory process was assessed by an experimental study which demonstrated higher values of high-sensitivity C-reactive protein (hs-CRP) in patients with NA-AION [35].

The favorable visual results were associated with few side-effects during follow-up. As in previous studies using intra-ocular steroids, ocular hypertension was observed in the present series. Mean IOP was increased throughout the follow-up but never reached statistical significance except at 3 months, when the injected and the non-injected group was compared. In all but one patient, IOP never exceeded 21 mm Hg. The highest IOP value measured throughout the study was 25 mm Hg at 3 months; thus, no sight-threatening IOP rise was observed in comparison with other reports of intraocular steroid injection [17, 18].

This modest IOP rise is of great importance as high intra-ocular pressure is known to induce hypoperfusion which is harmful for the optic nerve head already fragile in NA-AION [28, 29, 34, 36]. The low rate of steroid-induced ocular hypertension observed in the present study in comparison with other reports could be explained by systematic topical treatment of brinzolamide during the 3 months following the injection.

Although the visual benefit in NA-AION patients treated with IVTA was observed in the present series, the results must be considered with caution, considering the natural history of this disease with a spontaneous improvement of visual function. In addition, the retrospective, non-randomized character of this study simply provides preliminary data. Only a large randomized, controlled trial could make it possible to confirm the potential visual benefit of IVTA in NA-AION.

Conflicts of Interest None

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