

Results of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy in Inflammatory Choroidal Neovascularization

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Abstract

Purpose: To report the visual outcomes of intravitreal (IVT) anti-vascular endothelial growth factor (anti-VEGF) in inflammatory choroidal neovascularization (iCNV).

Methods: A retrospective study of 43 eyes of 38 patients with active choroidal neovascularization (CNV) related to ocular inflammatory disease, treated with IVT injections of anti-VEGF (bevacizumab, ranibizumab, or aflibercept), with or without associated systemic anti-inflammatory therapy, at Fattouma Bourguiba University Hospital, Monastir, Tunisia (24 eyes of 23 patients) and at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy (19 eyes of 15 patients) from January 1, 2013, to December 31, 2018.

Results: The mean age was 35.5 ± 16.4 years. The sex ratio male:female was 0.27. Seventeen eyes (39.5%) of 17 patients (44.7%) had only anti-VEGF injections, and 26 eyes (60.5%) of 21 patients (45.3%) had anti-VEGF injections and associated systemic anti-inflammatory therapy. Bevacizumab was injected in 36 eyes (83.7%), ranibizumab in six eyes (14%), and aflibercept in one eye (2.3%). Mean follow-up was 20.3 ± 19.2 months (range, 6–106 months). Mean visual acuity improved from 0.8 ± 0.37 logMAR (approximate Snellen equivalent 20/125) to 0.51 ± 0.42 logMAR (approximate Snellen equivalent 20/63) ($P < 0.001$). Mean central macular thickness on optical coherence tomography decreased from 403.7 ± 121.9 to 293.7 ± 82.8 μm ($P < 0.001$). Mean gain of vision was 2.9 ± 3.1 lines. The mean number of injections was 2.5. Twenty eyes (46.5%) received a single injection. There were no side effects related to the IVT injections of anti-VEGF.

Conclusions: CNV is a sight-threatening complication of uveitis. IVT anti-VEGF seems to be an effective and safe treatment for iCNV when inflammation is controlled.

Keywords: Anti-vascular endothelial growth factor injection, Bevacizumab, Choroidal neovascularisation, Optical coherence tomography, Ranibizumab, Uveitis

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INTRODUCTION

Choroidal neovascular membranes (CNVM) are a rare complication of uveitis with an incidence of 1.9%,¹ accounting for severe visual loss in young patients with ocular infectious or non-infectious inflammatory diseases.¹⁻³ Inflammatory choroidal neovascularization (iCNV) often occurs in eyes

with posterior uveitis or panuveitis.¹ Specific uveitic entities that are most commonly associated with the development of CNVM include multifocal choroiditis with panuveitis, punctate inner choroidopathy, serpiginous choroiditis, and Vogt-Koyanagi-Harada syndrome.¹⁻⁵ Various therapeutic

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modalities have been proposed for the management of iCNV, including argon-laser photocoagulation, photodynamic therapy, local and systemic corticosteroids, immunosuppressive agents, and surgical excision.² These therapeutic modalities have potential limitations and are associated with a high rate of complications and recurrences.² Recently, intravitreal (IVT) anti-vascular endothelial growth factor (anti-VEGF) has been found to be effective in the management iCNV.³ However, most studies are small retrospective case series,⁶⁻²⁵ and there is still no established treatment regimen for IVT anti-VEGF injections in this setting. The purpose of the current study was to assess the anatomical and functional results of anti-VEGF injections with or without associated anti-inflammatory treatments in a relatively large number of patients with iCNV from two referral centers in the Mediterranean area.

METHODS

The medical records of 38 patients (43 eyes) diagnosed with active iCNV and treated with IVT anti-VEGF at Fattouma Bourguiba University Hospital, Monastir, Tunisia (24 eyes of 23 patients) and at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy (19 eyes of 15 patients) from January 1, 2013, to December 31, 2018, with a minimum follow-up of 6 months were retrospectively reviewed.

All patients underwent detailed ophthalmic examination, including best corrected Snellen visual acuity, slit-lamp assessment, intraocular pressure (IOP) measurement, funduscopy, laser flare photometry, fluorescein angiography (FA), spectral domain optical coherence tomography (OCT), and indocyanine green angiography, in selected patients. Two patients underwent swept source OCT angiography. The diagnosis of active choroidal neovascularization (CNV) was made based on fundus biomicroscopy findings (grayish-yellow lesion associated with retinal hemorrhages, intraretinal or subretinal fluid or hard exudates), FA results (early hyperfluorescence with late leakage), and OCT findings (subretinal hyperreflective lesion related to a CNVM complex associated with subretinal or intraretinal fluid, which was considered to be indicative of active iCNV).

Patients with inactive iCNV, CNVM of non-inflammatory origin, and iCNV not treated with IVT injection of anti-VEGF were excluded. The off-label use of the drug and its potential risks and benefits as well as other treatment options were discussed extensively with all patients (or their guardians) who read and signed informed consent. A single IVT anti-VEGF (bevacizumab 1.25 mg/0.05 ml [$n = 36$], ranibizumab 0.5 mg/0.05 ml [$n = 6$], and aflibercept 2 mg/0.05 ml [$n = 1$]) was performed at the first diagnosis of iCNV and was injected using a 27G needle in a sterile manner, 3.5–4 mm posterior to the limbus, through the inferotemporal pars plana after topical anesthesia and povidone instillation in the eye. Bevacizumab aliquots were prepared in the hospital pharmacies. IOP and retinal artery perfusion was checked immediately after the injection. In pediatric cases, the dose

was given in the operating room under general anesthesia. Oral corticosteroids (oral prednisone 0.5–1 mg/kg/day for 15–30 days, then gradually tapered) were given in cases of active uveitis associated with anti-infectious therapy in patients with infectious uveitis. Conventional immunosuppressive therapy was used as steroid sparing agents in case of corticosteroid dependence, corticosteroid resistance, or side effects related to corticosteroid therapy. Immunosuppressive drugs used were methotrexate (10–25 mg/week), azathioprine (2.5 mg/kg/day), and cyclosporine (2–5 mg/kg/day). Best corrected visual acuity (BCVA) was assessed using Snellen charts and listed as logMAR equivalents. Patients were examined at 1 day and 1 month after the first injection and monthly thereafter. Follow-up examinations included BCVA, slit-lamp examination, IOP measurement, funduscopy, OCT, and occasionally, FA. Reinjections were administered as needed on the basis of a pro re nata (PRN) protocol when there was evidence of persistent or recurrent activity evaluated by funduscopy and OCT examination (intraretinal and/or subretinal fluid).

The study protocol followed the tenets of the declaration of Helsinki and was approved by the local institutional review board.

Statistical analyses were performed using the SPSS software version 21 (SPSS, Inc., Chicago, IL, USA). Non-parametric tests (Mann–Whitney *U*-test, Wilcoxon test, and Spearman's rank correlation test) were used. The primary outcomes of our study included posttreatment BCVA and posttreatment central macular thickness (CMT). $P < 0.05$ was considered statistically significant.

RESULTS

Mean age was 35.5 years \pm 16.4 ([range, 8–73 years], 82% under 50 years). There were eight males and 30 females. The mean duration of uveitis before current therapy was 27 \pm 24 months (range, 1–312 months). Uveitis was active in 28 eyes (65.1%) and inactive in 15 eyes (34.9%) at the time of CNV. Uveitis was bilateral in 32 patients (84.2%) and unilateral in six patients (15.8%). Specific etiological diagnoses of uveitis included punctate inner choroidopathy ($n = 12$) [Figure 1], ocular sarcoidosis ($n = 8$), ocular toxoplasmosis ($n = 5$) [Figure 2], serpiginous choroiditis ($n = 5$), Vogt-Koyanagi-Harada disease ($n = 3$), ocular histoplasmosis-like syndrome ($n = 2$) [Figure 3], endogenous endophthalmitis ($n = 2$), and presumed ocular tuberculosis ($n = 1$). The mean size of CNVM, assessed on early-phase FA, was 0.99 \pm 1.04 disc diameters (range, 0.125–6 disc diameters). The neovascular membrane was uniformly type 2 (classic) in nature, with subfoveal location in 28 eyes (62.2%), juxtafoveal location in eight eyes (17.8%), extrafoveal location in three eyes (6.7%), and peripapillary location in six eyes (13.3%) ($n = 45$). One eye had three separate foci of CNVM. Nine patients (23.7%) had bilateral CNV [Table 1].

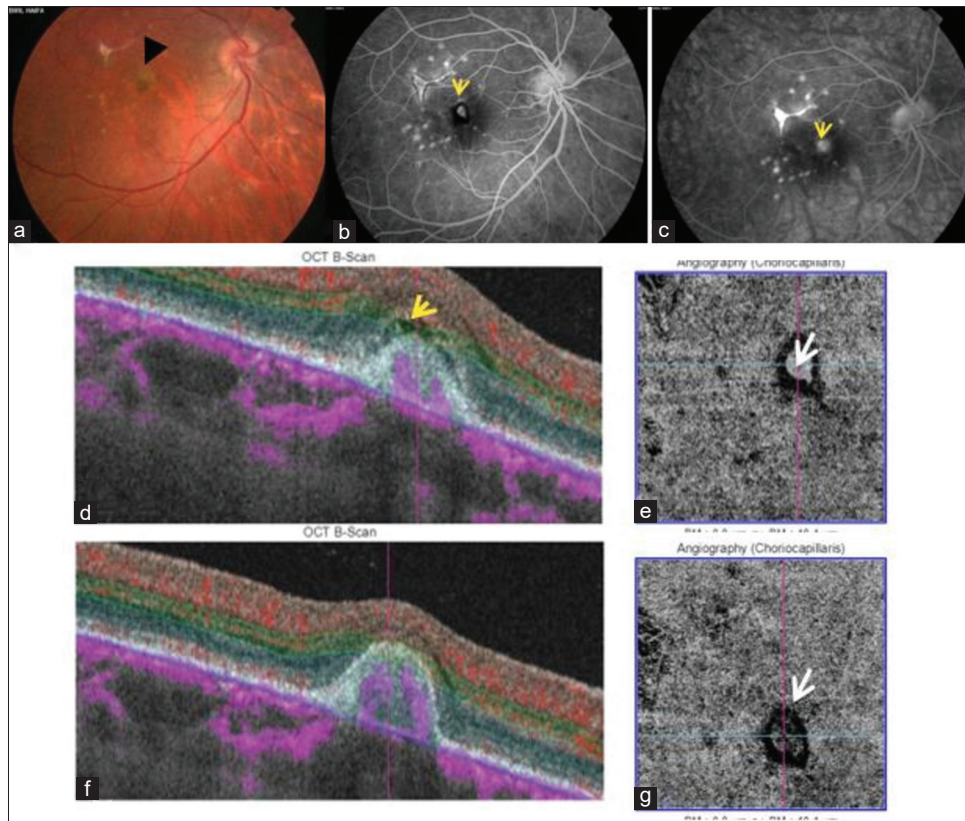


Figure 1: (a) Fundus photograph of the right eye of a 27-year-old female patient with punctate inner choroidopathy shows a greyish subretinal lesion (arrowhead). Early-phase (b) and late-phase (c) fluorescein angiograms show leakage due to choroidal neovascularization (arrow). (d) Optical coherence tomography (OCT) B-scan shows a fusiform subretinal hyperreflective lesion (arrow) associated with the presence of intraretinal fluid and serous macular detachment. (e) OCT angiography 3 mm × 3 mm scan of the outer retina and choriocapillaris confirms the presence of a choroidal neovascular membrane (CNVM) (arrow). OCT B-scan (f) and OCT angiography (g) 1 month after a single intravitreal injection of bevacizumab shows a decrease in the size of CNVM with a decrease in vessel caliber and branching, and resolution of serous macular detachment

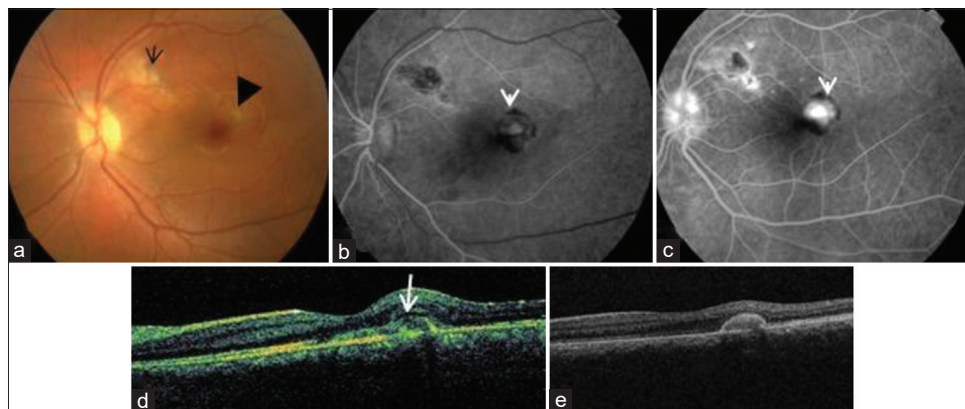


Figure 2: (a) Color fundus photograph of a 16-year-old female patient with a history of ocular toxoplasmosis shows an atrophic chorioretinal scar (black arrow), and a slightly prominent greyish subretinal lesion, superotemporal to the fovea (white arrowhead). (b) Early-phase fluorescein angiogram shows hyperfluorescent, well-defined juxtafoveal choroidal neovascular membrane (CNVM) surrounded by retinal hemorrhages (white arrowhead). (c) Late-phase fluorescein angiogram shows a profuse leakage from the neovascular membrane (white arrowhead). (d) Optical coherence tomography (OCT) shows a fusiform subretinal hyperreflective lesion, corresponding to the CNVM (white arrow) associated with the presence of intraretinal fluid. (e) OCT, 18 months after a single intravitreal injection of bevacizumab shows a subretinal hyperreflective dome-like lesion without intraretinal fluid, consistent with inactive scar

Seventeen eyes (39.5%) of 17 patients (44.7%) received only IVT bevacizumab, and 26 eyes (60.5%) of 21 patients (42.3%)

were treated with IVT anti-VEGF (bevacizumab [$n = 19$], ranibizumab [$n = 6$], aflibercept [$n = 1$]) associated to systemic

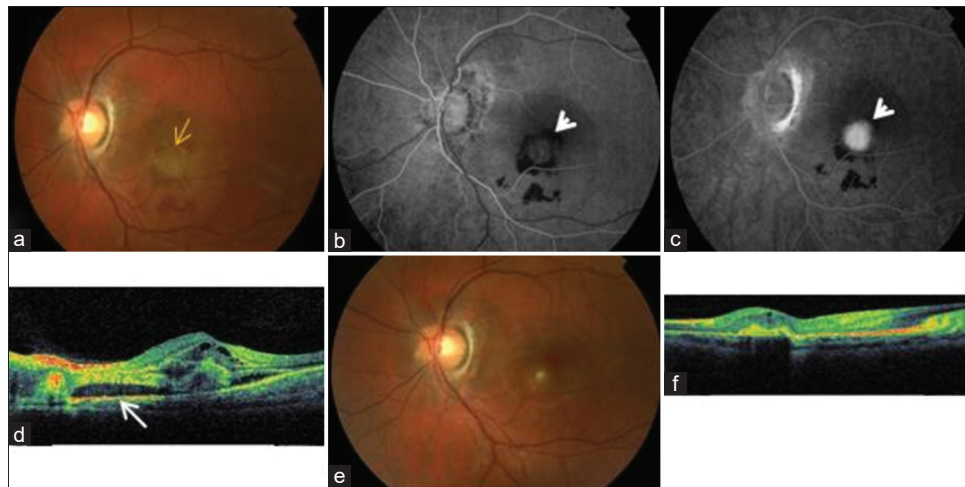


Figure 3: (a) Fundus photograph of the left eye of a 27-year-old female patient with ocular histoplasmosis-like syndrome shows a greyish subretinal lesion with retinal hemorrhages (yellow arrow). Early-phase (b) and late-phase (c) fluorescein angiograms show leakage due to choroidal neovascularization (arrowhead). (d) Optical coherence tomography (OCT) shows a subretinal hyperreflective lesion corresponding to the choroidal neovascular membrane seen on fluorescein angiography with associated serous macular detachment, retinal thickening, and cystoid spaces (white arrow). (e) Fundus photograph 12 months after a single intravitreal injection of bevacizumab shows disappearance of retinal hemorrhages with residual subretinal fibrosis. (f) OCT shows resolution of serous macular detachment with persistence of a small retinal cyst

immunosuppressive agents (oral corticosteroids in all cases and a conventional immunosuppressant in four patients) [Table 1]. After a mean follow-up of 20.3 ± 19.2 months, the mean number of IVT injections was 2.5 (range, 1–13). Twenty eyes (46.5%) received one injection, nine eyes (21%) received two injections, six eyes (14%) received three injections, and eight eyes received more than three injections (18.5%). A switch from one anti-VEGF to another was not performed in our study. No adverse event related to anti-VEGF or to the injection procedure was observed [Table 1].

In the whole group of patients, mean BCVA improved 2.9 ± 3.1 lines from 0.8 ± 0.37 logMAR (approximate Snellen equivalent 20/125) to 0.51 ± 0.42 logMAR (approximate Snellen equivalent 20/63) ($P < 0.001$). BCVA improved 1–3 lines in 14 eyes (32.6%), 4–6 lines in 6 eyes (14%), and more than six lines in nine eyes (20.7%). BCVA remained unchanged in 11 eyes (25.6%) and worsened in three eyes (7%). Mean CMT decreased significantly from 403.7 ± 121.9 μm at baseline (range, 240–831 μm) to 293.7 ± 82.8 μm (range, 147–536 μm) ($P < 0.001$) [Table 2]. Among eyes treated with bevacizumab ($n = 36$, 83.7%), BCVA improved 1–3 lines in 12 eyes (33.3%), 4–6 lines in five eyes (13.9%), and more than 6 lines in eight eyes (22.2%). It remained unchanged in nine (25%) eyes and worsened in two eyes (5.6%) after a mean of 2.4 injections (range, 1–13). Mean BCVA improved three lines, from 0.8 ± 0.39 logMAR (approximate Snellen equivalent 20/125) to 0.5 ± 0.36 logMAR (approximate Snellen equivalent 20/63) ($P < 0.001$). Mean CMT decreased significantly from baseline 420 ± 125.6 μm (range, 240–831 μm) to 287 ± 83.1 μm (range, 147–536 μm) ($P < 0.001$) [Table 2].

Analysis of the punctate inner choroidopathy group revealed significant improvement in visual acuity ($P = 0.039$) with a significant decrease in CMT ($P = 0.03$) after a mean

of 3.1 injections of bevacizumab associated to systemic immunosuppressive treatment in 13 eyes (92.8%) of 11 patients (91.7%). Analysis of the sarcoidosis group revealed significant improvement in visual acuity ($P = 0.043$) with a significant decrease in CMT ($P = 0.018$) after a mean of 2.5 injections of bevacizumab associated to systemic immunosuppressive treatment in five eyes (62.5%) of five patients (62.5%). Analysis of the toxoplasmosis group revealed significant improvement in visual acuity ($P = 0.043$) without a significant decrease in CMT ($P = 0.109$) after a mean of 1.2 injections of bevacizumab. Analysis of the Vogt-Koyanagi-Harada group revealed significant improvement in visual acuity ($P = 0.042$) without a significant decrease in CMT ($P = 0.068$) after a mean of four injections of bevacizumab associated to systemic immunosuppressive treatment in four eyes (80%) of two patients (66.6%). Analysis of the serpiginous choroiditis, ocular histoplasmosis-like syndrome, endogenous endophthalmitis, and tuberculosis groups revealed improvement in visual acuity with a decrease in CMT, but results were not significant. A subfoveal location of the CNVM and a size >1 disc diameter was significantly associated with poor final visual acuity ($P = 0.046$, $P = 0.04$, respectively). However, the visual improvement did not correlate with the patient's age, size or location of CNV, presence of active uveitis, type of anti-VEGF used, or the primary inflammatory disease.

DISCUSSION

This is a relatively large series of patients with iCNV from two referral centers in the Mediterranean region. IVT anti-VEGF drugs associated or not with local or systemic anti-inflammatory therapy resulted in a significant visual and anatomical improvement with a low incidence of recurrence and no complications.

Table 1: Demographic and clinical characteristics of 38 patients (43 eyes) with inflammatory choroidal neovascularization

Study period	January 2013-December 2018
Total patients (total eyes)	38 patients (43 eyes)
Age (years)	
Mean	35.5
Range	8-73
Male:female	8:30
Uveitis (number of eyes) (%)	
Active	28 (65.1)
Inactive	15 (34.9)
Etiology (number of patients) (%)	
Punctate inner choroidopathy	12 (31.6)
Sarcoidosis	8 (21.1)
Toxoplasmosis	5 (13.2)
Serpiginous choroiditis	5 (13.2)
Vogt-Koyanagi-Harada disease	3 (7.9)
Ocular histoplasmosis-like syndrome	2 (5.3)
Endogenous endophthalmitis	2 (5.3)
Presumed ocular tuberculosis	1 (2.6)
Location of CNVM (number of eyes) (%)	
Subfoveal	28 (62.2)
Juxtafoveal	8 (17.8)
Extrafoveal	3 (6.7)
Peripapillary	6 (13.3)
CNVM size (disc diameters)	
Mean	0.99
Range	0.125-6
Treatment of the CNVM (number of eyes) (%)	
Anti-VEGF injections alone	17 (39.5)
Anti-VEGF injections associated with systemic anti-inflammatory therapy	26 (60.5)
Type of anti-VEGF used (number of eyes) (%)	
Bevacizumab	36 (83.7)
Ranibizumab	6 (14)
Aflibercept	1 (2.3)
Mean number of injections (range)	2.5 (1-13)
Total follow-up (months), mean±SD	20.3±19.2

CNVM: Choroidal neovascular membranes, VEGF: Vascular endothelial growth factor, SD: Standard deviation

Table 2: Visual and anatomical outcomes of inflammatory choroidal neovascular membrane after anti-vascular endothelial growth factor therapy

	BCVA (logMAR, mean) (Snellen equivalent)	CMT (mean, range) μ m
In the whole group (n=43 eyes)		
Pretreatment	0.8 (20/125)	404 (240-831)
Final visit	0.51 (20/63)	293 (147-536)
Mean gain	2.9	111
P	<0.001	<0.001
Eyes treated with bevacizumab (n=36 eyes, 83.7%)		
Pretreatment	0.8 (20/125)	420 (240-831)
Final visit	0.5 (20/63)	287 (147-536)
Mean gain	3	133
P	<0.001	<0.001

BCVA: Best corrected visual acuity, CMT: Central macular thickness

Results of our study, consistent with previous data, show that the iCNV was uniformly classic, subfoveal in location in the majority of our cases (62.2%), small in size (<1 disc diameter),

and associated with panuveitis or posterior uveitis in most cases.¹⁻⁸ The most common specific cause of inflammatory CNVM in our case series was punctate inner choroidopathy

accounting for 31.6%, which is consistent with the majority of previous studies.^{1-3,6} However, we found a high rate of ocular sarcoidosis (21%) compared to literature.¹⁻⁸ In our case series, uveitis was active in most eyes (65.1%) at the time of CNV development, whereas Mansour *et al.* in a retrospective study of 99 eyes found 75% of cases with inactive uveitis.⁶ Choroidal neovascular proliferation seems to result from chronic inflammation with sustained release of inflammatory cytokines and/or VEGF production. Inflammatory CNV usually develops at the vicinity of choroiditis/retinochoroiditis scars due to disruptions of the choriocapillaris–Bruch’s membrane–retinal pigment epithelium (RPE) complex there. VEGF is a potent mediator of pathologic angiogenesis that acts in consortium with other chemical mediators resulting in CNV.^{26,27} Therefore, IVT injection of anti-VEGF could be a treatment approach directly affecting the pathogenic pathway of CNVM formation without causing collateral damage. Among 43 eyes included in this study treated with IVT anti-VEGF with or without associated systemic anti-inflammatory treatment, mean BCVA improved 2.9 lines, and mean CMT decreased significantly from baseline 420 μm to 287 μm ($P < 0.001$) after a mean follow-up of 20.3 months with a mean of 2.5 injections. Many series of inflammatory CNV treated with VEGF antagonists had shown the effectiveness and safety of IVT anti-VEGF in the treatment of iCNV.⁶⁻²⁵ However, bevacizumab is currently off-label for IVT use, that is why before the injection of bevacizumab, the patient should sign a specific informed consent. In our case series, the mean number of injections was 2.5. In literature, the mean number of anti-VEGF injections varied between 1 and 4.25 injections.^{6,12,13,17,23,24} Most clinical studies, as well as our report, used PRN regimen.^{6,12,13,17,23,24} A study by Invernizzi *et al.* has shown that a loading phase of three 3 monthly injections followed by PRN re-treatment does not confer any advantage in terms of visual outcomes as compared to PRN regimen from the start.²⁸ Re-injections were recommended when there was a recurrence, evaluated by funduscopy, and OCT examination. Previous studies have shown some beneficial effect of corticosteroids and immunosuppressives alone on the control of iCNV mainly in eyes with severe intraocular inflammation related to the decrease of cytokine release involved in angiogenesis.²⁻²⁷ However, recent data have shown greater anatomical results and visual improvement with anti-VEGF injections indicated at the first diagnosis of iCNV, particularly those involving or close to the fovea. Associated clinical or subclinical active intraocular inflammation is controlled at the same time to boost anti-VEGF efficacy, prevent iCNV recurrences, and reduce the need for re-injections.³⁻²⁹ Future studies are needed to determine the optimum dosing sequence for IVT and the role of switching between anti-VEGF drugs in refractory iCNV. Furthermore, the literature showed that iCNV needs much fewer IVT injections than age-related macular degeneration related CNV to achieve the complete regression of the membrane because of numerous factors: iCNV are classic in type and small in size, the angiostatic effect of periocular or systemic corticosteroids in iCNV, younger age of subjects with iCNV, and a generally

healthy RPE.^{6,23} Some side effects are reported to be associated with IVT injection of bevacizumab, especially endophthalmitis and cardiovascular complications.^{30,31} In our study, no adverse event was observed.

In our report, patients with CNV secondary to ocular toxoplasmosis had significantly better visual improvement than other causes of iCNV ($P = 0.049$). A subfoveal location of the CNVM and a size >1 disc diameter were significantly associated with poor final visual acuity. The visual improvement did not correlate with patient age, size or location of CNV, presence of active uveitis, type of anti-VEGF, or primary disease. However, in the literature, visual improvement correlated significantly with the size of the CNV and the primary disease.⁶ In fact, the visual improvement was better in eyes with ocular histoplasmosis-like syndrome, punctate inner choroidopathy, and ocular toxoplasmosis than other causes of iCNV.^{6,11,18} Poor long-term visual prognosis may be secondary to submacular fibrosis, central macular edema, or spread of chorioretinal atrophy.^{32,33}

Limitations of our study include the retrospective design, heterogeneity in anti-VEGF agents and in immunomodulatory therapies received, and the absence of a standardized protocol for treatment and follow-up. The heterogeneity in the treatment approaches and the absence of a standardized protocol reflect the real-life nature of the study.

In conclusion, anti-VEGF therapy seems to be an effective treatment modality allowing a significant BCVA improvement and significant foveal flattening in a wide variety of iCNV without side effects. Systemic anti-inflammatory therapy, including steroids, immunosuppressive therapy, or biological agents, should be associated in case of concomitant active uveitis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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