

# Intravitreal bevacizumab for choroidal neovascularisation in serpiginous choroiditis

M Battaglia Parodi,<sup>1</sup> P Iacono,<sup>2</sup> C La Spina,<sup>1</sup> K A Knutsson,<sup>1</sup> A Mansour,<sup>3</sup>  
J F Arevalo,<sup>4,5</sup> F Bandello<sup>1</sup>

<sup>1</sup>Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele, Milano, Italy

<sup>2</sup>Department of Ophthalmology, Fondazione G. B. Bietti per l'Oftalmologia, IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico), Rome, Italy

<sup>3</sup>Department of Ophthalmology, American University of Beirut, Rafic Hariri University Hospital, Beirut, Lebanon

<sup>4</sup>The Retina Division, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

<sup>5</sup>The King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia

## Correspondence to

Dr Pierluigi Iacono, Department of Ophthalmology, Fondazione G. B. Bietti per l'Oftalmologia, IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico), Via Livenza 3, Rome 00198, Italy; pierluigi.iacono@libero.it

Received 27 August 2013

Revised 5 December 2013

Accepted 16 December 2013

Published Online First

10 January 2014

## ABSTRACT

**Purpose** To assess the effects of intravitreal bevacizumab (IVB) in the treatment of choroidal neovascularisation (CNV) secondary to serpiginous choroiditis (SC).

**Design** Non-randomised, interventional case series.

**Participants** Seven patients (seven eyes) affected by juxtafoveal CNV (six eyes) and subfoveal CNV (one eye) associated with SC were recruited.

**Methods** Each patient underwent an ophthalmological examination, including measurement of best-corrected visual acuity (BCVA), fluorescein angiography (FA) and optical coherence tomography (OCT). After a first IVB injection (1.25 mg), patients were evaluated monthly over a 12-month follow-up. Further re-treatments were performed on the basis of detection of any type of fluid on OCT and/or presence of leakage on FA. The primary outcome considered was the median change in BCVA, as well as the proportion of eyes gaining at least 5 and 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at the end of the 12-month follow-up. Secondary outcomes included median changes in central macular thickness (CMT) and number of injections over the planned follow-up.

**Results** Median BCVA changed from 0.3 to 0.4 LogMAR. A functional improvement of at least 5 and 10 ETDRS letters was obtained in two eyes (28%) and one eye (14%), respectively, at the 12-month examination. Four eyes (57%) had stable BCVA, whereas one eye (14%) experienced a two-line decrease. Median CMT at baseline was 261 µm, decreasing to 196 µm at the 12-month examination. The median number of IVB injections was 1 in 12 months.

**Conclusions** IVB can achieve anatomical stabilisation of CNV secondary to SC, avoiding a decline in visual acuity, in almost 90% of cases over a 12-month follow-up.

## INTRODUCTION

Serpiginous choroiditis (SC) is a rare, usually bilateral, progressive, recurrent, inflammatory disorder, primarily affecting the inner choroid, choriocapillaris and retinal pigment epithelium.<sup>1–5</sup>

SC is most frequently characterised by peripapillary involvement, with centrifugal progression in a geographic pattern. Even though SC is idiopathic in most cases and is not associated with other conditions, several authors have highlighted the relationship between SC and infectious disorders, especially tuberculosis.<sup>6–9</sup>

Visual acuity impairment may be related to the progressive foveal extension of the serpiginous lesion, the development of pigment epithelial hyperplasia or fibrosis, and the occurrence of

choroidal neovascularisation (CNV).<sup>10</sup> In particular, CNV can occur in as many as 25% of cases, leading to severe visual deterioration.<sup>10–13</sup> Many treatment options have been proposed for SC-related CNV, including laser photocoagulation, photodynamic therapy and surgical excision, with patchy results.<sup>10–12</sup> Recently, a few cases have been treated with anti-vascular endothelial growth factor (VEGF) drugs, with promising outcomes.<sup>13–18</sup>

The present study examines the 12-month outcome of CNV secondary to SC treated with intravitreal bevacizumab (IVB).

## METHODS

The study was designed as a prospective, interventional case series, with a planned follow-up of 12 months. All the consecutive patients referred to our centres for the diagnosis and management of CNV secondary to SC were prospectively enrolled in the study. The research was approved by the institutional review boards and adhered to the tenets of the Declaration of Helsinki. Each patient was carefully informed about the purpose of the research, providing signed consent to all procedures.

Inclusion criteria were diagnosis of SC, evidence of CNV and best-corrected visual acuity (BCVA) of at least 20/320. Exclusion criteria were features and conditions other than SC, any other ocular disease that could compromise vision in the study eye, pregnancy, uncontrolled systemic hypertension, and peripheral vascular disease and history of thromboembolism or stroke.

Each patient underwent a systemic work-up and an ophthalmological examination, including measurement of BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, slit-lamp biomicroscopy, fluorescein angiography (FA) and optical coherence tomography (OCT).

After an initial IVB injection (1.25 mg), all patients were re-evaluated every month over a 12-month follow-up. The patients were examined on a monthly basis, including BCVA measurement and OCT, whereas FA was performed every 3 months, or more frequently, at the ophthalmologist's discretion. Further re-treatments were performed on the basis of the detection of any type of fluid on OCT and/or presence of leakage on FA.

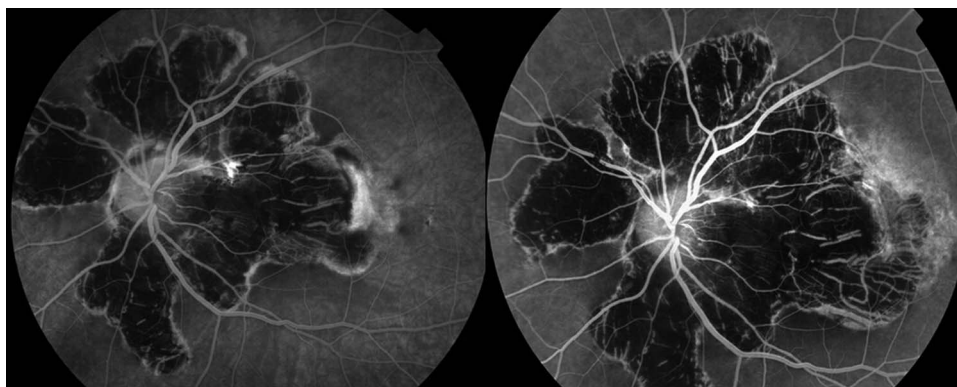
The primary outcome measure was the median change in BCVA and also the proportion of eyes gaining at least 5 and 10 letters (1 and 2 ETDRS lines) at the end of the 12-month follow-up.

Secondary outcomes included the changes in central macular thickness (CMT) and number of injections over the planned follow-up.



CrossMark

**To cite:** Parodi MB, Iacono P, La Spina C, et al. *Br J Ophthalmol* 2014;**98**:519–522.



**Figure 1** Fluorescein angiography at baseline showing a juxtafoveal choroidal neovascularisation (CNV) associated with late staining of the margin of the macular lesion indicating the activity of the inflammatory process (left side). At 3 months after a single intravitreal bevacizumab injection, the stabilisation of the juxtafoveal CNV is associated with an inactive chorioretinal scar that, however, showed a greater spreading in comparison to the baseline (right side).

## RESULTS

Overall, seven patients (seven eyes) referred for severe visual acuity deterioration due to CNV occurrence in SC and fulfilling the inclusion and exclusion criteria were recruited for the study. The patients had a median age of 46 (mean  $46.2 \pm 10.5$  years), with six females and one male.

All the patients were initially diagnosed with SC and treated in other centres. In detail, two patients underwent previous treatment with triple therapy (prednisone (1 mg/kg/day), cyclosporin (5 mg/kg/day, initially) and azathioprine (1.5 mg/kg/day)), while five patients received alkylating agents: chlorambucil (with an initial dose of 2 mg/day) and cyclophosphamide (2 mg/kg/day). Laboratory tests for tuberculosis, syphilis, toxoplasmosis and herpetic infections were performed in all cases, with negative results. In particular, QuantiFERON testing and chest X-rays were negative in all cases.

At baseline none of the patients was receiving therapy because SC was judged to be quiescent.

Clinical examination revealed active SC in one case (figure 1). CNV was classic-type in all cases, located juxtafoveally in six eyes and subfoveally in one eye (table 1).

Oral cyclophosphamide therapy (150 mg/day) was initiated in the single case showing reactivation of the disease.

Mean BCVA was  $0.5 \pm 0.34$  LogMAR (approximately corresponding to 20/63 Snellen equivalent) (median 0.3 LogMAR, approximately corresponding to 20/40 Snellen equivalent) at baseline and  $0.48 \pm 0.38$  LogMAR (approximately corresponding to 20/50 Snellen equivalent) (median 0.4, approximately corresponding to 20/50 Snellen equivalent) at the end of the follow-up. A functional improvement of at least 5 and 10

ETDRS letters was obtained in two eyes (28%) and one eye (14%), respectively, at the 12-month examination. Four eyes (57%) had stable BCVA, whereas one eye (14%) experienced a two-line decrease.

Mean CMT was  $254 \pm 22$   $\mu\text{m}$  at baseline (median CMT 261  $\mu\text{m}$ ), decreasing to  $196 \pm 5$   $\mu\text{m}$  (median 196  $\mu\text{m}$ ) at the 12-month examination ( $p < 0.001$ ). Mean maximum macular thickness was  $268 \pm 23$   $\mu\text{m}$  (median 269) at baseline and  $205 \pm 6$   $\mu\text{m}$  (median 207) at the end of the follow-up ( $p < 0.001$ ).

No fluorescein leakage and no haemorrhages were detectable at the end of the follow-up. In addition, no patient initially presenting juxtafoveal CNV displayed subfoveal involvement over the follow-up and at the final visit. The mean number of IVB injections was  $1.5 \pm 1.51$  (median 1; range 1–5) at the end of 12 months. No systemic or ocular side effects were registered over the follow-up.

## DISCUSSION

SC is a progressive disease in which multiple recurrences lead to a severe loss of visual acuity, especially when the fovea is involved.<sup>1–7 10</sup> More specifically, the functional deterioration can be caused by the inflammatory lesion extending to the fovea or by the development of chorioretinal atrophy, fibrous metaplasia and CNV.<sup>10</sup> CNV has been reported in up to 25% of cases, appearing in different locations.<sup>1–7 10</sup>

The pathogenesis of CNV associated with SC is complex, probably resulting from the combined effects of many factors. Chronic inflammation almost certainly plays a crucial role through the activation of macrophages and other inflammatory cells, which produce molecules causing the degradation of

**Table 1** Clinical data of patients with CNV associated with serpiginous choroiditis

Case	Age	CNV Location	Initial BCVA	Final BCVA	Initial CMT	Final CMT	Initial MMT	Final MMT	# injections
1	40	Juxtafoveal	0.4	0.4	261	205	287	216	5
2	41	Subfoveal	1	1	269	200	269	200	1
3	35	Juxtafoveal	1	1	287	199	299	211	1
4	67	Juxtafoveal	0.2	0	241	196	254	207	1
5	48	Juxtafoveal	0.3	0.2	220	195	230	207	1
6	46	Juxtafoveal	0.3	0.3	240	188	255	201	1
7	46	Juxtafoveal	0.3	0.5	266	190	285	198	1

BCVA, best-corrected visual acuity (expressed as LogMAR); CMT, central macular thickness; CNV, choroidal neovascularisation; MMT, maximum macular thickness.

Bruch's membrane. The cytokines released by these inflammatory cells may also promote the growth of CNV through the degenerated Bruch's membrane into the subretinal pigment epithelium space.<sup>19–25</sup> Indeed, VEGF overexpression has been demonstrated in samples of active CNV secondary to inflammatory chorioretinal disorders.<sup>25–26</sup>

The recent introduction of anti-VEGF molecules in the management of CNV has been extended to inflammatory CNVs, with several studies reporting positive results for both subfoveal and juxtafoveal CNV.<sup>13–18 27–30</sup>

In order to try to assess the effects of IVB for CNV associated with SC, we designed a pilot study with a 12-month follow-up. The results achieved are interesting from several points of view.

First of all, even though IVB ensured anatomical stabilisation of the CNV, as demonstrated by both a reduction in CMT and the cessation of fluorescein leakage, BCVA did not show significant benefits, with almost 60% of eyes displaying no change. Thus, although IVB can be useful in halting the CNV growth and exudation, this approach does not guarantee any significant functional improvement. Positive outcomes in the treatment of CNVs related to inflammatory conditions, even including SC, have also been achieved by means of systemic anti-inflammatory and immunosuppressive therapy.<sup>6 24 31–34</sup> Systemic treatment can lead to the progressive stabilisation of the CNV, toning down the chronic inflammatory drive. Nevertheless, bearing in mind the potential side effects related to the systemic therapy, a treatment based solely on an anti-VEGF approach has its attractions in the management of SC-related CNVs. All patients in our case series had previously undergone systemic therapy, achieving SC quiescence. However, at the baseline examination, only one case showed active SC and was treated with cyclophosphamide, whereas the remaining patients, who did not reveal any signs of inflammation, received merely the anti-VEGF injection. It is theoretically possible that a combined therapy of systemic anti-inflammatory or immunosuppressive drugs with anti-VEGF could lead to a better visual outcome, merging the effect on the underlying inflammatory disease with the direct action on the CNV.

It is noteworthy that the number of IVB injections required to achieve the stabilisation of the CNV was remarkably low. This response seems to be a characteristic of inflammatory CNVs and may be ascribable to a number of factors, such as the classic-type nature of the condition and the smaller size of the CNV, together with the younger age of the patients involved.<sup>13–18 27–30</sup>

Our study has many obvious limitations, the most prominent being the small number of patients and the absence of a control group. Nevertheless, SC is an infrequent disease and the detection of a CNV is even rarer. It is therefore unlikely that a randomised clinical trial with sufficient statistical power could ever be designed in the near future.

In essence, this prospective case series shows that IVB can result in anatomical stabilisation of CNV secondary to SC but is unable to contribute to an improvement in visual acuity.

**Contributors** Conception and design: MBP and PI; analysis and interpretation, final approval of the article, and provision of materials, patients or resources: MBP, PI, CLaS, KAK, AM, JFA and FB; writing the article: MBP, PI, CLaS, AM, JFA and FB; critical revision of the article: MBP, PI and FB; data collection: CLaS, KAK, AM and JFA; statistical expertise: PI, MBP, CLaS and AM; and literature research: CLaS, KAK, AM and JFA.

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** Institutional review boards of the University Vita-Salute, Scientific Institute San Raffaele, Milano, Italy.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

- Hamilton AM, Bird AC. Geographic choroidopathy. *Br J Ophthalmol* 1984;58:784–97.
- Buggage RR, Nusseblatt RB. Serpiginous choroiditis. *Surv Ophthalmol* 2005;50:231–44.
- Weiss H, Annesley WH Jr, Shields JA, et al. The clinical course of serpiginous choroidopathy. *Am J Ophthalmol* 1979;87:133–42.
- Christmas NJ, Oh KT, Oh DM, et al. Long-term follow-up of patients with serpiginous choroiditis. *Retina* 2002;22:550–6.
- Jampol LM, Orth D, Daily MJ, et al. Subretinal neovascularization with geographic (serpiginous) choroiditis. *Am J Ophthalmol* 1979;88:683–9.
- Khanamiri NH, Rao NA. Serpiginous choroiditis and infectious multifocal serpiginoid choroiditis. *Surv Ophthalmol* 2013;58:203–32.
- Vasconcelos-Santos DV, Rao PK, Davies JB, et al. Clinical features of tuberculous serpiginouslike choroiditis in contrast to classic serpiginous choroiditis. *Arch Ophthalmol* 2010;128:853–8.
- Mahendradas P, Kamath G, Mahalakshmi B, et al. Serpiginous choroiditis-like picture due to ocular toxoplasmosis. *Ocul Immunol Inflamm* 2007;15:127–30.
- Priya K, Madhavan HN, Reiser BJ, et al. Association of herpesviruses in the aqueous humor of patients with serpiginous choroiditis: a polymerase chain reaction based study. *Ocul Immunol Inflamm* 2002;10:247–61.
- Gass JDM. *Stereoscopic atlas of macular diseases: diagnosis and treatment*. St. Louis: Mosby-Year Book Inc, 1997:158–64.
- Kuo IC, Cunningham ET Jr. Ocular neovascularization in patients with uveitis. *Int Ophthalmol Clin* 2000;40:111–26.
- Park SP, Ko DA, Chung H, et al. Photodynamic therapy with verteporfin for juxta foveal choroidal neovascularization in serpiginous choroiditis. *Ophthalmic Surg Lasers Imaging* 2006;37:425–8.
- Mansour AM, Mackensen F, Arevalo JF, et al. Intravitreal bevacizumab in inflammatory ocular neovascularization. *Am J Ophthalmol* 2008;146:410–16.
- Mansour AM, Arevalo JF, Ziemssen F, et al. Long-term visual outcomes of intravitreal bevacizumab in inflammatory ocular neovascularization. *Am J Ophthalmol* 2009;148:310–16.e2.
- Song MH, Roh YJ. Intravitreal ranibizumab for choroidal neovascularisation in serpiginous choroiditis. *Eye* 2009;23:1873–5.
- Julián K, Terrada C, Fardeau C, et al. Intravitreal bevacizumab as first local treatment for uveitis-related choroidal neovascularization: long-term results. *Acta Ophthalmol* 2011;89:179–84.
- Parodi MB, Iacono P, Verbraak FD, et al. Antivascular endothelial growth factors for inflammatory chorioretinal disorders. *Dev Ophthalmol* 2010;46:84–95.
- Rouvas A, Petrou P, Douvali M, et al. Intravitreal ranibizumab for the treatment of inflammatory choroidal neovascularization. *Retina* 2011;31:871–9.
- Chevalley G, Brazitikos PD, Paccolat F, et al. Uveitis complicating posterior segment neovascularization. Six cases. *Klin Monbl Augenheilkd* 1992;200:382–5.
- Oh H, Takagi H, Takagi C, et al. The potential angiogenic role of macrophages in the formation of choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1999;40:1891–8.
- Dhingra N, Kelly S, Majid MA, et al. Inflammatory choroidal neovascular membrane in posterior uveitis. Pathogenesis and treatment. *Indian J Ophthalmol* 2010;58:3–10.
- Kinnunen K, Yla-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med* 2012;44:1–17.
- van Wijngaarden P, Qureshi SH. Inhibitors of vascular endothelial growth factor (VEGF) in the management of neovascular age-related macular degeneration: a review of current practice. *Clin Exp Optom* 2008;91:427–37.
- Baxter SL, Pistilli M, Pujari SS, et al. Risk of choroidal neovascularization among the uveitides. *Am J Ophthalmol* 2013;156:468–77.e2.
- Vinore SA, Youssri AI, Luna JD, et al. Upregulation of vascular endothelial growth factor in ischemic and non-ischemic human and experimental retinal disease. *Histol Histopathol* 1997;12:99–109.
- Shimada H, Yuzawa M, Hirose T, et al. Pathological findings of multifocal choroiditis with panuveitis and punctuate inner choroidopathy. *Jpn J Ophthalmol* 2008;52:282–8.

- 27 Parodi MB, Iacono P, Kontadakis DS, *et al.* Bevacizumab vs photodynamic therapy for choroidal neovascularization in multifocal choroiditis. *Arch Ophthalmol* 2010;128:1100–3.
- 28 Parodi MB, Iacono P, Mansour A, *et al.* Intravitreal bevacizumab for juxtafoveal choroidal neovascularization secondary to multifocal choroiditis. *Retina* 2013;33:953–6.
- 29 Parodi MB, Iacono P, Bandello F. Juxtafoveal choroidal neovascularisation secondary to persistent placoid maculopathy treated with intravitreal bevacizumab. *Ocul Immunol Inflamm* 2010;18:399–401.
- 30 Kilmartin DJ, Forrester JV, Dick AD. Cyclosporine-induced resolution of choroidal neovascularization associated with sympathetic ophthalmia. *Arch Ophthalmol* 1998;116:249–50.
- 31 Dees C, Arnold JJ, Forrester JV, *et al.* Immunosuppressive treatment of choroidal neovascularization associated with endogenous posterior uveitis. *Arch Ophthalmol* 1998;116:1456–61.
- 32 Neri P, Manoni M, Fortuna C, *et al.* Association of systemic steroids and mycophenolate mofetil as rescue therapy for uveitic choroidal neovascularization unresponsive to the traditional immunosuppressants: interventional case series. *Int Ophthalmol* 2010;30:583–90.
- 33 Akpek EK, Jabs DA, Tessler HH, *et al.* Successful treatment of serpiginous choroiditis with alkylating agents. *Ophthalmology* 2002;109:1506–13.
- 34 O'Toole L, Tufail A, Pavesio C. Management of choroidal neovascularization in uveitis. *Int Ophthalmol Clin* 2005;45:157–77.