

# Ranibizumab for subfoveal choroidal neovascularisation associated with Stargardt disease

Maurizio Battaglia Parodi,<sup>1</sup> Marion R Munk,<sup>2,3</sup> Perluigi Iacono,<sup>4</sup> Francesco Bandello<sup>1</sup>

<sup>1</sup>Department of Ophthalmology, University Vita-Salute, San Raffaele Hospital, Milan, Italy

<sup>2</sup>Department of Ophthalmology, Medical University of Vienna, Vienna, Austria

<sup>3</sup>Department of Ophthalmology, Inselspital, University Hospital Bern, Bern, Switzerland

<sup>4</sup>Fondazione G. B. Bietti per l'Oftalmologia, IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico), Rome, Italy

## Correspondence to

Dr Marion R Munk,  
Department of Ophthalmology;  
Inselspital, University Hospital  
Bern, Bern, Switzerland,  
Freiburgstrasse 4, Bern 3010,  
Switzerland;  
marion\_munk@hotmail.com

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## ABSTRACT

**Introduction** To describe the clinical outcomes of intravitreal ranibizumab treatment for subfoveal choroidal neovascularisation (CNV) associated with Stargardt disease.

**Methods** Prospective, interventional, case series. All patients underwent intravitreal ranibizumab injections following a pro re nata regimen with monthly examination, over a 24-month follow-up.

**Results** Three eyes were included in the study. Best corrected visual acuity changed from  $0.47 \pm 0.06$  (mean  $\pm$  SD) at baseline to  $0.90 \pm 0.17$  LogMAR at the end of the 24-month follow-up. Overall, a mean number of 11 ranibizumab injections were administered in 24 months. Significant atrophic growth was detected in all cases, with the mean atrophy area increasing from  $2.34 \pm 2.60$  mm<sup>2</sup> (mean  $\pm$  SD) at baseline to  $4.23 \pm 3.31$  mm<sup>2</sup> at the end of the follow-up.

**Conclusions** Ranibizumab treatment can stop the CNV progression, but cannot ensure a significant visual improvement. Macular atrophy tends to significantly enlarge under ranibizumab treatment over the follow-up.

## INTRODUCTION

Stargardt disease (STGD) is a retinal dystrophy characterised by progressive lipofuscin accumulation within retinal pigment epithelium (RPE) cells leading to increased background and yellow fleck.<sup>1</sup> Visual acuity impairment is mostly related to the progressive degeneration of the central RPE and the photoreceptor cells. Atrophic changes of the macula are characteristic for late stages of the disease, leading usually to a deterioration of visual acuity as severe as 20/200 or worse.<sup>2</sup> The occurrence of choroidal neovascularisation (CNV) associated with STGD is rare, but can lead to further visual acuity loss.<sup>3–6</sup> Owing to the rarity of the CNV development complicating a relatively infrequent dystrophy, such as STGD, limited information is currently available in terms of its therapeutic management.<sup>3–6</sup> The aim of the present study is to describe the morphological-functional outcomes after ranibizumab treatment for subfoveal CNV associated with STGD, over a 24-month follow-up.

## METHODS

The study design was approved by the institutional review board, and all the procedures were conducted in accordance with the Declaration of Helsinki. All patients referred for clinical evaluation and management and affected by CNV associated with STGD, were included in the study. The patients were carefully informed about the purpose of the investigation, and signed a written informed consent.

The patients underwent a baseline ophthalmological examination consisting of best corrected visual acuity (BCVA) measurement using standard Early Treatment Diabetic Retinopathy Study charts, fluorescein angiography (FA), short-wavelength fundus autofluorescence (SW-FAF) and optical coherence tomography (OCT).

FA, 477 nm SW-FAF imaging and OCT were performed using Spectralis HRA instruments (Heidelberg Engineering, Heidelberg, Germany). The study protocol included a monthly examination with BCVA measurement and OCT assessment, whereas FA was repeated every 3 months. High-resolution volume-scans with 30 automatic real time averaging frames centred foveolarly were performed. Using the follow-up function, OCT scans were generated at the same retinal location at every visit. Areas of low SW-FAF signal corresponding to atrophic changes in the RPE were manually measured using the instrument's image analysis software.

The patients underwent ranibizumab intravitreal injection at baseline, and followed a pro re nata re-treatment regimen based on the detection of fluid on OCT and/or leakage on FA. All data are given as mean and SD (mean  $\pm$  SD)

## RESULTS

The study included three patients who were followed up monthly over 24 months. Molecular analyses confirmed the mutations in ACA4 gene (A1598D in patient 1, and G1961E in patient 2 and 3). Main clinical data of the three cases are reported in table 1. Patient 1 was affected by a bilateral CNV, with the fellow eye showing a disciform scar; patient 2 was monocular due to a corneal leucoma related to a previous trauma in the fellow eye; patient 3 was unilaterally affected by CNV (figure 1). All the included eyes were affected by subfoveal, predominantly classic CNV.

Mean BCVA was  $0.47 \pm 0.06$  LogMAR (mean  $\pm$  SD) at baseline and  $0.90 \pm 0.17$  LogMAR at the end of the follow-up. Mean central retinal thickness reduced from  $730 \pm 120$  microns (mean  $\pm$  SD) to  $314 \pm 81$  microns at the 2-year examination.

Overall, a mean number of  $7 \pm 1$  (mean  $\pm$  SD) ranibizumab injections were administered at 12 months, which increased to  $11 \pm 2.5$  (mean  $\pm$  SD) at the end of the follow-up. At the 24-month examination, CNV showed no activity in two cases, whereas the third case, disclosing intraretinal fluid and leakage, was advised to undergo further treatment. OCT examination revealed the presence of subretinal hyper-reflective material above the CNV along with hyper-reflective dots in all the cases at baseline, which progressively resolved. Moreover,



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**Table 1** Clinical data of three cases of choroidal neovascularization associated with Stargardt disease treated with intravitreal ranibizumab over a 24-month follow-up

|        | Baseline BCVA (LogMAR) | Final BCVA (LogMAR) | Baseline CRT ( $\mu$ ) | Final CRT ( $\mu$ ) | Baseline atrophy ( $\text{mm}^2$ ) | Final atrophy ( $\text{mm}^2$ ) | Number of injections at 12 months | Number of injections at 24 months |
|--------|------------------------|---------------------|------------------------|---------------------|------------------------------------|---------------------------------|-----------------------------------|-----------------------------------|
| Case 1 | 0.5                    | 1                   | 591                    | 407                 | 5.2                                | 7.61                            | 7                                 | 9                                 |
| Case 2 | 0.5                    | 0.7                 | 805                    | 254                 | 0.10                               | 1                               | 6                                 | 11                                |
| Case 3 | 0.4                    | 1                   | 795                    | 283                 | 1.73                               | 4.09                            | 8                                 | 14                                |

BCVA, best corrected visual acuity; CRT, central retinal thickness.

outer retinal tubulations (ORTs) developed in all cases over time. The measurement of subfoveal choroidal thickness revealed a reduction from a baseline value of 156 microns, to a final value of 134 microns.

During the course of the follow-up all the eyes disclosed an overall enlargement of RPE atrophy. In detail, mean RPE atrophy was  $2.34 \pm 2.60 \text{ mm}^2$  at baseline and  $4.23 \pm 3.31 \text{ mm}^2$  at 24 months (figures 1 and 2).

## DISCUSSION

The aim of the present study was to evaluate the effects and efficacy of intravitreal ranibizumab for the management of CNV associated with STGD. All the patients included in our study revealed a final visual acuity deterioration, associated with enlargement of the atrophic areas and significant choroidal thickness decrease.

The natural evolution of CNV complicating STGD can lead to a disciform scar, which further reduces the visual function.<sup>1 2</sup> According to the time period and the availability of specific treatments, variable therapeutic options including observation, laser photocoagulation and photodynamic therapy have been tried, unfortunately achieving overall unsatisfactory outcomes.<sup>2-4</sup> The recent advent of anti-vascular endothelial growth factor (VEGF) treatments has also been extended to CNV complicating dystrophies with encouraging results.<sup>5-7</sup> However, our prospective case

series of CNV associated with STGD shows that visual function does not benefit from ranibizumab treatment over a 24-month follow-up. In addition, the number of injections required over 12 months and 24 months exceeded that normally required for the management of dystrophy-related CNV,<sup>5-7</sup> resulting more similarly to that normally required for the management of CNV secondary to age-related macular degeneration (AMD).<sup>8</sup> It is also noteworthy that the enlargement of atrophic changes at the posterior pole which was identified in all the three eyes, seems to go beyond that normally detectable in AMD.<sup>9 10</sup> Further evidence of the enlargement of the atrophic changes may be represented by the development of ORT in all of the three eyes which also indicate that anti-VEGF treatment may aggravate the growth of atrophy in STGD. The incidence of ORTs in retinal dystrophies is less than 10%,<sup>11</sup> and increases as the zones of atrophy enlarge.<sup>11</sup> Their incidence also increases after anti-VEGF treatment.<sup>12</sup>

RPE cells engulfed with lipofuscin may be more prone to further degenerative processes related to the effects of anti-VEGF molecules. In particular, some evidence exists that anti-VEGF molecules may exert a harmful effect on RPE and choriocapillaris. Mice lacking the soluble forms of VEGF developed choroidal and RPE loss, ie, changes that resemble atrophic AMD.<sup>13</sup> Moreover, the neutralisation of VEGF in cultured RPE led to increased cell death, and VEGF neutralisation in vivo resulted in damage to the RPE-choroid complex, including

**Figure 1** Top: Short-wavelength fundus autofluorescence of Patient 3 at baseline. The white arrow in the right eye indicates the location of the subfoveal choroidal neovascularisation which appears hyper-autofluorescent. Both eyes show atrophic areas. Bottom: SD-optical coherence tomography (OCT) of the right eye revealing the choroidal neovascularisation with fluid and several hyper-reflective dots.

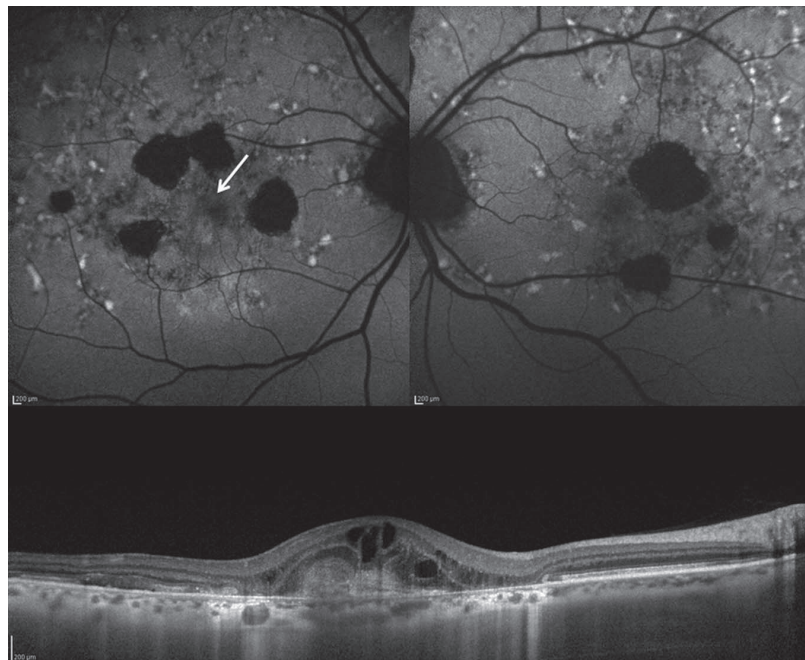
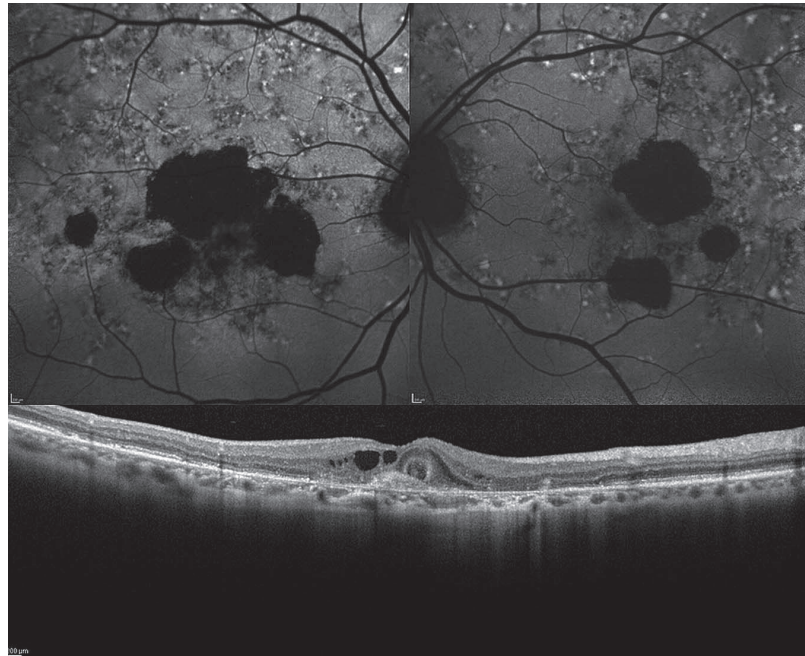


**Figure 2** Top: Short-wavelength fundus autofluorescence of the same patient at the 24-month examination. The atrophy in the right eye has remarkably enlarged, a limited growth is detectable in the left eye. Bottom: SD-optical coherence tomography (OCT) of the right eye at 24 month visit disclosing persistent presence of fluid, together with outer retinal tubulations and hyper-reflective dots.



vacuolisation, loss of association with photoreceptor outer segments, and decreased choriocapillaris fenestrations.<sup>14</sup> The presence of ORT in our patients at baseline, may imply an ongoing degenerative process related to the disease itself, which could be further worsened by the VEGF inhibition, with accelerated atrophic changes as final evolution.

The high re-treatment rate may suggest that VEGF blockage with ranibizumab is rather insufficient to control the CNV activity. This implies that other pathogenic mechanisms and factors beyond VEGF may be involved. In particular, as shown in an in vitro model, A2E can stimulate the RPE production and release many inflammatory chemokines, which are directly involved in angiogenesis and vasopermeability.<sup>15</sup> The OCT detection of sub-retinal hyper-reflective material associated with hyper-reflective dots may be interpreted as the indirect manifestation of an inflammatory reaction related to these biochemical alterations. A more comprehensive approach for CNV associated with STGD might be required, combining anti-VEGF therapy with other therapeutic approaches, in order to achieve a neuroprotective effect, and the control of the inflammatory response. Further studies are warranted to define the best treatment for STGD-related CNV.

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**Competing interests** FB is an advisory board member for Novartis Pharmaceuticals Corporation.

**Patient consent** Obtained.

**Ethics approval** University Vita-Salute, San Raffaele Hospital, Milan, Italy.

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## REFERENCES

- Battaglia Parodi M. Eredodistrofie Corioretiniche. Rome: Verduci Editore, 2002:21–60.
- Rotenstreich Y, Fishman GA, Anderson RJ. Visual acuity loss and clinical observations in a large series of patients with Stargardt disease. *Ophthalmology* 2003;110:1151–8.
- Klein R, Lewis RA, Meyers SM, et al. Subretinal neovascularisation associated with Fundus flavimaculatus. *Arch Ophthalmol* 1978;96:2054–7.
- Valmaggia C, Niederberger H, Helbig H. Photodynamic therapy for choroidal neovascularization in fundus flavimaculatus. *Retina* 2002;22:111–13.
- Pawlak D, Souied E, Mimoun G, et al. Fundus flavimaculatus and choroidal neovascularisation. *J Fr Ophthalmol* 2006;29:188–94.
- Querques G, Bocco MC, Soubrane G, et al. Intravitreal ranibizumab (Lucentis) for choroidal neovascularization associated with Stargardt's disease. *Graefes Arch Clin Exp Ophthalmol* 2008;246:319–21.
- Battaglia Parodi M, Iacono P, Cascavilla M, et al. Intravitreal bevacizumab for subfoveal choroidal neovascularization associated with pattern dystrophy. *Invest Ophthalmol Vis Sci* 2010;51:4358–61.
- Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group/Martin DF, Maguire MG, Fine SLIII, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388–98.
- Grunwald J, Pistilli M, Gui-Shuang EEY, et al. Size and growth of geographic atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT). *ARVO* 2014, May 04, 1649.
- Grunwald JE, Daniel E, Huang J, et al. Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2014;121:150–61.
- Goldberg NR, Greenberg JP, Laud K, et al. Outer retinal tubulation in degenerative retinal disorders. *Retina* 2013;33:1871–6.
- Papastefanou VP, Nogueira V, Hay G, et al. Choroidal naevi complicated by choroidal neovascular membrane and outer retinal tubulation. *Br J Ophthalmol* 2013;97:1014–19.
- Saint-Geniez M, Kurihara T, Sekiyama E, et al. An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. *Proc Natl Acad Sci USA* 2009;106:18751–6.
- Ford KM, Saint-Geniez M, Walshe T, et al. Expression and Role of VEGF in the Adult Retinal Pigment Epithelium. *Invest Ophthalmol Vis Sci* 2011;52:9478–87.
- Anderson OA, Finkelstein A, Shima DT. A2E induces IL-1 $\beta$  production in retinal pigment epithelial cells via the NLRP3 inflammasome. *PLoS ONE* 2013;8:e67263.