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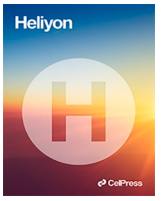

Research article

Could internal limiting membrane peeling before Voretigen neparvovec-ryzl subretinal injection prevent focal chorioretinal atrophy?

Lea Dormegny [a], Fouzia Studer [b], Arnaud Sauer [a], Laurent Ballonzoli [a], Claude Speeg-Schatz [a], Tristan Bourcier [a], Helene Dollfus [b], David Gaucher [a,*]

[a] Department of Ophthalmology, New Civil Hospital, Strasbourg University Hospital, Strasbourg, France
[b] Institut de Génétique Médicale d'Alsace, CARGO Reference Center for Rare Diseases in Genetic Ophthalmology, University Hospital of Strasbourg, Strasbourg, France

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ABSTRACT

Purpose: To report the effect of internal limiting membrane (ILM) peeling prior to Voretigen Neparvovec-ryzl (VN) subretinal injection on focal chorioretinal atrophy development in patients presenting with RPE65-mediated Leber congenital amaurosis (LCA).
Design: Retrospective case series.
Methods: Three patients who underwent bilateral subretinal VN injection for RPE65-mediated LCA were followed up for 18–24 months. ILM peeling was performed unilaterally in patients 1 and 2 and bilaterally in patient 3. Chorioretinal atrophy was identified on fundus biomicroscopy, non-mydriatic retinography and/or ultrawide field fundus imaging. Best corrected visual acuity (BCVA), spectral-domain optical coherence tomography (SD-OCT), visual fields, full-field stimulus threshold (FST) and visual functioning questionnaire score (NEI-VFQ-25) were reported. Outcome measures were changes in BCVA, visual fields, FST, NEI-VFQ-25, and chorioretinal atrophy location.
Results: Chorioretinal atrophy at the injection site exclusively developed in eyes which did not undergo prior ILM peeling. In patient 3, bilateral pre-operative nummular chorioretinal alterations progressed toward epithelial atrophic patches in the mid and extreme retinal periphery 18 months after VN injection. BCVA and visual fields improved bilaterally. NEI_VFQ 25 remained stable in patient 1 and improved in patient 2 and 3. FST test improved bilaterally in patient 3.
Conclusions: ILM peeling prior to VN injection seems to be a smoother and safer technique to administer VN treatment and may prevent secondary focal atrophy development at the injection site. However, another type of more extended chorioretinal atrophy might exist and could be related to LCA evolution or to incompletely understood adverse effect of VN product.

1. Introduction

Leber congenital amaurosis (LCA) is a rare inherited retinal affection (prevalence of 1/80,000) characterized by poor vision from birth with further decline to near complete blindness in early to mid-adulthood [1]. More than 25 genes are associated with LCA,

* Corresponding author. Centre Hospitalier Universitaire de Strasbourg 1, place de l'Hôpital 67000 Strasbourg, France.
E-mail address: david.gaucher@chru-strasbourg.fr (D. Gaucher).

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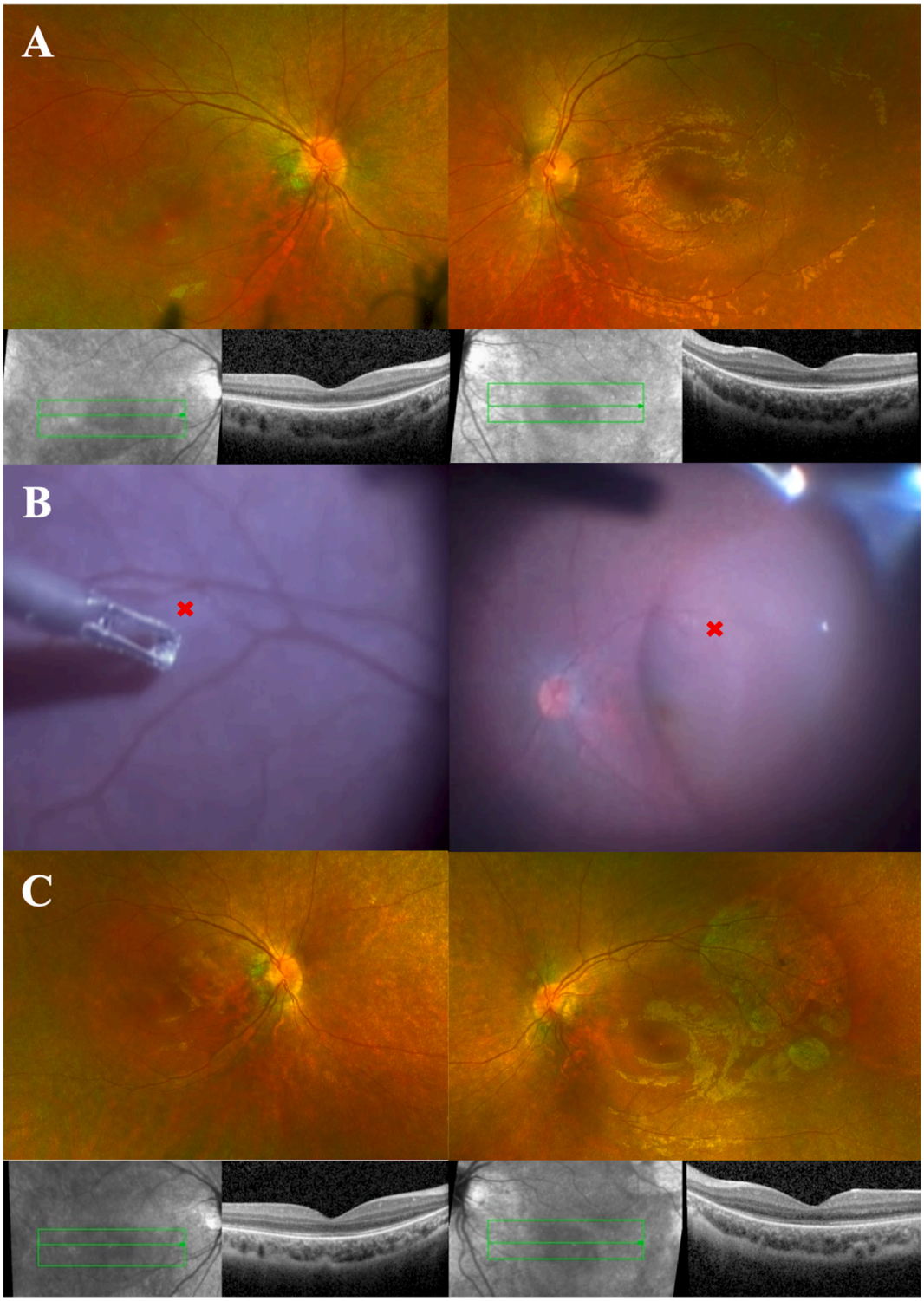

Fig. 1. Pre-, per-, and post-operative bilateral fundus imaging of patient 1. A. Pre-operative ultra-wide field fundus imaging (UWF) showing no chorioretinal atrophy. Corresponding spectral-domain optical coherence tomography (SD-OCT) below. B. Image capture of per-operative video records of Voretigene neparvovec-ryzl (VN) subretinal injection showing internal limiting membrane (ILM) peeling at the injection site in the right eye (left image). Right image shows post-injection subretinal bleb in the left eye. No previous peeling was performed in this eye. Red crosses indicate VN injection site. C. Three months post-operative UWF showing the development of chorioretinal atrophy, exclusively in the left eye (right image). The atrophic area is located at and slightly extends from the injection site. Right eye remains free of atrophy (left image). Corresponding SD-OCT below.

including RPE65 [2]. RPE65 is implicated in visual pigment regeneration by photoreceptor after light exposure. This function is completed by an isomerohydrolase, encoded by RPE65, that catalyzes the conversion of all-trans-retinyl esters to 11-cis-retinol in the retinoid cycle [3]. Recently, a novel gene therapy has been approved for the treatment of LCA with biallelic RPE65 mutation. Voretigene neparvovec-rzyl (VN) (Luxturna, Spark Therapeutics) is an adeno-associated virus 2 (AAV2) vector containing a functional copy of the RPE65 gene, which is injected into the subretinal space via pars plana vitrectomy, under a standardized protocol [4]. Improvements of multi-luminance mobility testing (MLMT) and full-field light sensitivity threshold (FST) were reported after VN injection, compared to controls [4]. Very few adverse events were reported following injections. Most of them, such as transient intraocular pressure elevations (18 %) or cataract (18 %), might be related to vitrectomy more than to subretinal injection itself [4,5]. Chorioretinal atrophy has recently been reported and might develop either within the treated areas [6,7] or, more extensively, around the vascular arcades and outside of the treated area [8,9]. After a mean follow-up period of one year, best corrected visual acuity (BCVA), FST and visual field seem not to be impaired by chorioretinal atrophy development [8]. One recent study even reported FST improvement in patients presenting with extensive chorioretinal atrophy [9]. However, the development of chorioretinal atrophy remains an issue of great concern, also in view of the high costs involved in this therapy.

This study reports the case of three LCA patients who received bilateral VN subretinal injection with a follow-up period of two years. Chorioretinal atrophy developed in one eye of two patients at the injection site area. Interestingly, in the other 4 eyes, the surgical injection technique was slightly modified by focal peeling of the internal limiting membrane (ILM) prior to subretinal injection and no focal chorioretinal atrophy was observed. Chorioretinal atrophy onset at the injection site and surgical VN subretinal injection technique might be related in these patients.

2. Methods

2.1. Patient selection and surgical procedures

A retrospective case series review was performed on three patients who received subretinal VN injection at the Strasbourg University Hospital (Strasbourg, France). The patients' data were collected as part of the PERCEIVE study. PERCEIVE (Novartis) is an ongoing global registry-based post-authorization study designed to evaluate the real-world long-term safety profile of VN and to assess visual function over 5 years. All patients provided consent or parental permission and assent was obtained, as applicable. This study adhered to the tenets of the Declaration of Helsinki. All patients underwent VN injection in both eyes. Two of them were operated on in September 2019 (patient 1 and 2), while the third patient received injections in May 2021 (patient 3). Procedures were performed according to the recommended protocol described by Russell et al. [4] with the following exception: focal ILM peeling was performed at the site of VN injection (*i.e.,* in the superotemporal quadrant near vascular arcades) in one eye for patient 1 and 2 and in both eyes for patient 3 (see Video clip 1). Intraocular pressure was monitored similarly in all injected eyes with a reduction of the infusion pressure to 10 mmHg prior to the product injection.

2.2. Outcomes

The main outcome of the study was to assess macular chorioretinal atrophy formation after subretinal VN injection. All patients underwent best corrected visual acuity (BCVA, logMAR) assessment, refractive error measurement, slit lamp examination, fundus biomicroscopy, non-mydriatic retinography (NMR) (Topcon Healthcare, France), ultra-wide field fundus imaging (UWF) (Optos PLC, Dunfermline, Scotland), spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany) and kinetic visual field (Octopus 900 perimetry, Haag Streit International, Koeniz, Switzerland) before and after VN injection. Patient 3 underwent full-field stimulus threshold (FST) test (Diagnosys LLC, Dublin, Ireland) before and after VN injection. However, this exam was only performed after VN injection in patient 1 and 2, as the device was not available before their intervention date. One questionnaire for subjective quality of life assessment (NEI-VFQ 25) was taken before surgery, and 3 and 6 months after surgery (Supplementary material 1). Patients 1 and 2 were followed up for two years and assessments were achieved before and 3, 6, 12, 18 and 24 months after surgery. Patient 3 was followed up for 18 months and assessments were achieved before and 3, 6 and 18 months after surgery. Chorioretinal atrophy formation was identified on fundus biomicroscopy and confirmed on complementary examinations (NMR, UWF and SD-OCT). Intraoperative photographs were used to compare atrophic areas' location with the original subretinal bleb position. Descriptive statistics were used to report data from this retrospective case series.

3. Results

Patient 1 was an 8-year-old hyperopic girl (refractive error of +1.75 on the right eye and +3.00 on the left eye) with no visible areas of atrophy at baseline (Fig. 1). Preoperative BCVA (logMAR) was +1.0 on the right eye and +1.0 on the left eye. A subretinal bleb involving the fovea was created in both eyes intraoperatively and focal ILM peeling was performed before VN injection on her right eye (Fig. 1 and Video clip 1). There was no per-operative complication. Within the first 3 months postoperatively, she presented with left unilateral chorioretinal atrophy (Fig. 1). Multiple focal macular atrophic areas developed along the arcades, one of them including the subretinal injection point. Atrophy progressed during the follow-up with progressive confluence of the areas (Fig. 2), while the right eye remained unaffected (Fig. 1). Atrophy remained into the area of the subretinal bleb. Fovea was not involved. Efficacy outcomes revealed slight improvement of BCVA after two years in both eyes (+0.8 logMAR on the right eye and +0.8 logMAR on the left eye). Post-operative visual fields demonstrated improvement (i.e., expansion and gain of isopters) in both eyes (Supplementary material

2A). After 24 months, mean red and blue FST was −0.99 ± 1.31 and −4.39 ± 0.67 on the right eye, respectively and 3.67 ± 0 and −2.99 ± 0.25 on the left eye, respectively (Supplementary material 3A). NEI-VFQ 25 scores for near activities, distance activities, social functioning, role difficulties, color vision and peripheral vision greatly increased at 3- and 6-months postoperatively.

Patient 2 was a 12-year-old hyperopic boy (refractive error of +2.25 on the right eye and +2.75 on the left eye) with no visible areas of atrophy at baseline (Fig. 3). Pre-operative BCVA (logMAR) was +0.4 on the right eye and +0.5 on the left eye. A subretinal bleb involving the fovea was created in both eyes intraoperatively and focal ILM peeling was performed before VN injection on his left eye. Intraretinal hemorrhage developed during the injection on the right eye. Nevertheless, bleeding was rapidly interrupted and proper quantity of VN could be injected in the subretinal space through a second injection site. Intra retinal blood completely resorbed only a few days after surgery. Within the first 3 months postoperatively, the patient presented with right unilateral chorioretinal atrophy on both VN injection sites. After two years of follow-up, the atrophic areas remained stable, no other retinal alteration was observed, therefore, the fovea was never involved (Fig. 3). Efficacy outcomes revealed slight improvement of BCVA on the right eye (+0.3 logMAR) and stable BCVA (+0.5 logMAR) on the left eye. Post-operative visual fields demonstrated improvement (*i.e.,* expansion and gain of isopters) in both eyes. Notably paracentral scotomas disappeared three months postoperatively in both eyes (Supplementary material 2B). After 24 months, mean red and blue FST was 2.29 ± 1.56 and −1.65 ± 0.16 on the right eye, respectively and 3.67 ± 0 and −1.84 ± 0.12 on the left eye, respectively (Supplementary material 3B). NEI-VFQ 25 scores for near activities, distance activities, social functioning, role difficulties, color vision and peripheral vision did not improve in this patient.

Patient 3 was a 25-year-old hyperopic woman (refractive error of +2.50 on the right eye and +0.50 on the left eye) with bilateral nummular chorioretinal alterations in mid and extreme retinal periphery at baseline (Fig. 4). Preoperative BCVA (logMAR) was +2.3 on the right eye and +2.3 on the left eye. A subretinal bleb involving the fovea was created in both eyes intraoperatively and focal ILM peeling was performed before VN injection in both eyes. There was no per-operative complication. No focal atrophy developed at the injection site in both eyes. However, progression of the pre-operative nummular chorioretinal alterations toward epithelial atrophic patches was noted between 6- and 18-months visits (Fig. 4). BCVA (logMAR) remained stable postoperatively (+2.3 on the right eye and +2.3 on the left eye). Central visual fields remained stable after 18 months while moderate improvement was found in the superior

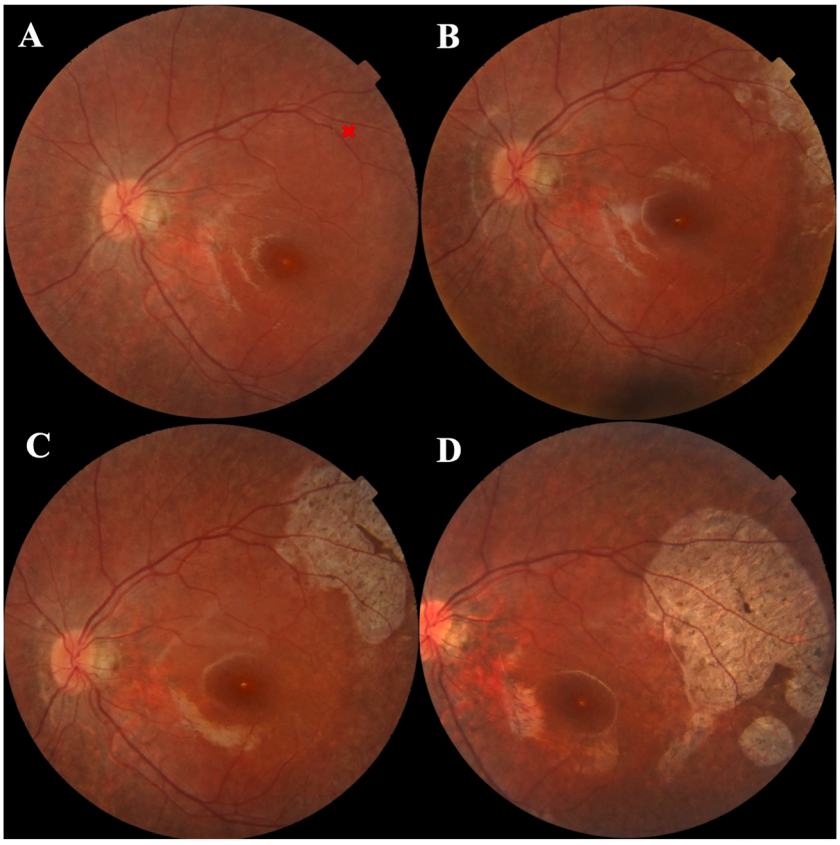

Fig. 2. Pre- and post-operative non-mydriatic retinographies (NMR) of the left eye of patient 1, in which subretinal Voretigene neparvovec-ryzl (VN) injection was performed without previous internal limiting membrane (ILM) peeling at the injection site. A. Pre-operative NMR showing the absence of chorioretinal atropy at and around the injection site (red cross). B. Three months post-operative NMR showing chorioretinal atrophy starting at the injection site with slight extension around. C. Six months post-operative NMR showing further extension of chorioretinal atrophy towards mid retinal periphery. D. One year post-operative NMR showing further temporal and posterior extension of chorioretinal atrophy, staying around the injection site and within the area of the per-operative subretinal bleb.

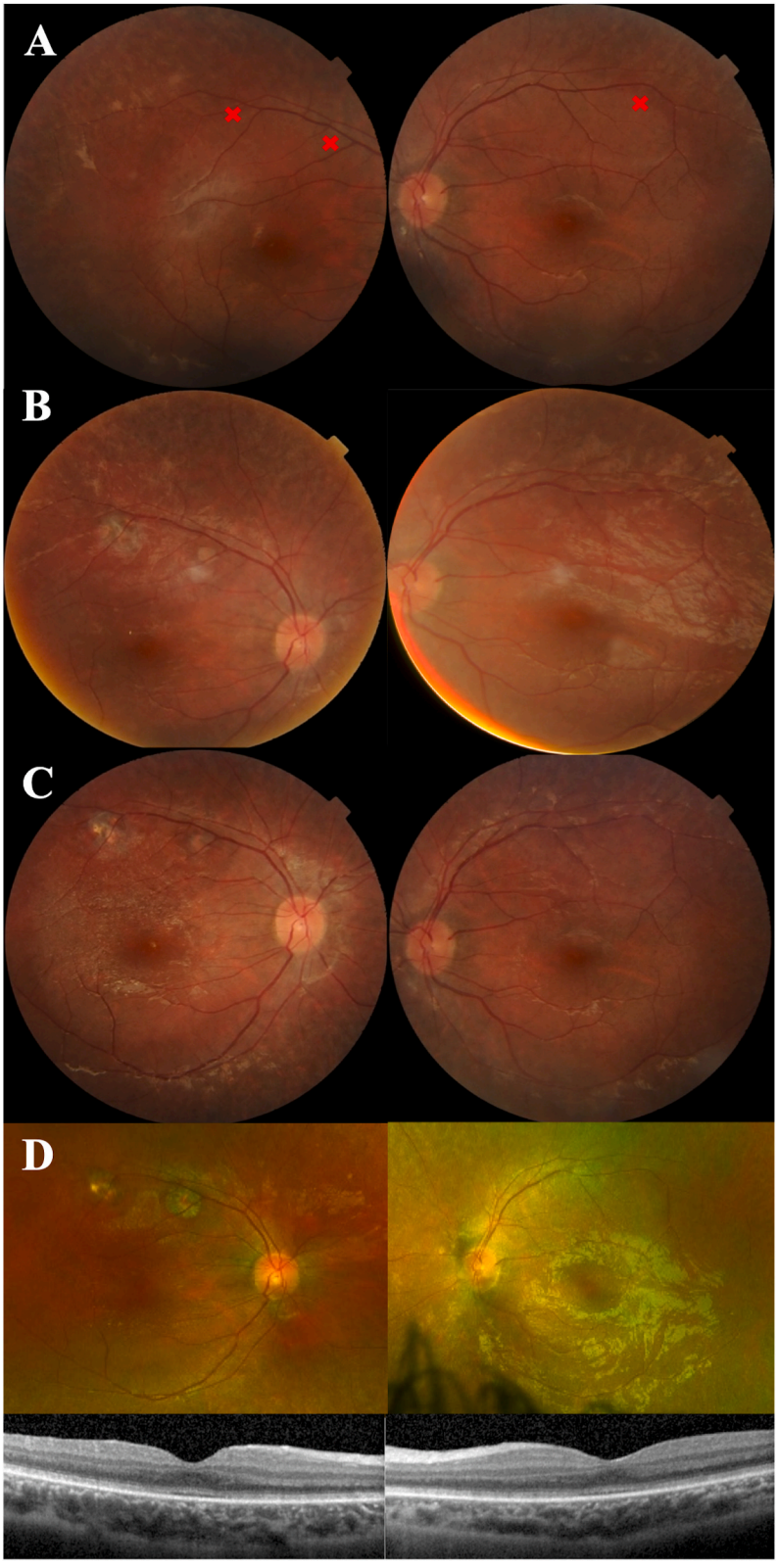

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Fig. 3. Pre- and post-operative non-mydriatic retinographies (NMR) and ultra-wide field fundus imaging (UWF) of both eyes of patient 2. Red crosses show Voretigene neparvovec-ryzl (VN) injection site. Internal limiting membrane (ILM) peeling was performed at the injection site in the left eye only. A. Pre-operative NMR showing no chorioretinal atropy in both eyes. B. Three months post-operative NMR showing chorioretinal atrophy at both injection sites in the right eye (left image). Left eye remains free of atrophy (right image). C. Six months post-operative NMR showing no further extension of chorioretinal atrophy in the right eye (left image). Left eye remains free of atrophy (right image). D. One-year post-operative UWF showing stable chorioretinal at both injection sites in the right eye (left image). Left eye remains free of atrophy (right image). Corresponding spectral-domain optical coherence tomography (SD-OCT) below.

quadrant in both eyes (Supplementary material 2C). Preoperatively, mean red and blue FST was -0.59 ± 0.35 and -0.65 ± 0.25 on the right eye, respectively and -0.75 ± 0.23 and -0.81 ± 0.04 on the left eye, respectively. After 18 months, mean red and blue FST was -1.76 ± 0.17 and -4.01 ± 0.14 on the right eye, respectively and -1.59 ± 0.13 and -3.92 ± 0.27 on the left eye, respectively (Supplementary material 3C and D). Changes in red and but FST were -1.18 ± 0.19 and -0.84 ± 0.09 on the right eye, respectively and -3.36 ± 0.11 and -3.11 ± 0.23 on the left eye, respectively. NEI-VFQ 25 scores for near activities, distance activities, social functioning, role difficulties, color vision and peripheral vision greatly increased at 3- and 6-months postoperatively.

4. Discussion

The present study reports unilateral perifoveal chorioretinal atrophy in two patients (patient 1 and 2) within three months following bilateral VN injection. Atrophy progressed markedly in one of them. Both patients underwent ILM peeling at the injection site in their fellow eye (See Video clip 1), which remained free of any atrophy after two years of follow-up. The third patient (patient 3), who underwent bilateral and focal ILM peeling before VN injection, developed no macular atrophy and no atrophy at the injection site 18 months after VN injection. However, multiple spots of patchy chorioretinal atrophy in the mid and extreme retinal periphery were noted and likely corresponded to an aggravation of pre-operative epithelial alterations. BCVA remained stable and visual field improved in all patients after injection, even in eyes presenting a progression of atrophy. FST test improved bilaterally in the third patient. Subjective NEI_VFQ 25 remained stable in the patient 1 and improved in patient 2 and 3.

These results demonstrate that, in both affected eyes, chorioretinal atrophy did not affect the expected visual and functional outcome after subretinal VN injection [6,8,10]. The absence of visual alteration in the presence of such chorioretinal atrophy has already been reported. In the first study describing this complication, FST and visual acuity did not significantly change in eyes presenting with atrophy. However, in this study, three out of the 18 affected eyes experienced related paracentral scotomas, which was not the case in our patients [8]. Interestingly, the development of extensive chorioretinal atrophy outside of the treated area correlated with FST improvement in one recent study, mostly in young adulthood patients, as observed in patient 3 in the present study [9].

There are many hypotheses that could be raised to explain chorioretinal atrophy development after VN injection. In our study, ocular progression of LCA is not likely to be responsible, as chorioretinal atrophy developed only in one eye in both patient 1 and 2. It might have played a role in patient 3 who developed bilateral extensive patchy atrophy in the periphery of the retina. The sequential apparition of the atrophy within only several months after VN injection suggests that chorioretinal atrophy may be related to VN secondary effect. Indeed, it is hypothesized that direct toxicity of the AAV2 vector to the photoreceptors and retinal pigment epithelium (RPE) could be responsible for atrophy development [8]. Indeed, Xiong et al. [11]. studied the ocular toxicity of various AAV vectors in mice and found dose-dependent RPE loss and outer nuclear layer thinning. The mild progression of nummular chorioretinal alterations towards patchy atrophy in patient 3 may be an example of this toxicity, although it has recently been associated to VN product efficacy and photoreceptor rescue with significant improvement of FST [9]. It is impossible though to rule out a simple progression of the disease in this case, as even none treated patients can evolve to patchy atrophy in LCA disease. In the first two patients of our study, unlike patient 3, atrophy is not likely to be related to direct toxicity of AAV2 vector as an equal concentration of product was injected in both eyes by the same surgeon, while atrophy developed unilaterally, only at the injection site. Post-operative intra-ocular inflammation, which has been reported in a variable proportion of patients following VN injection (8–11.1 %) might be another explanation for secondary chorioretinal atrophy [5,8]. However, in our study, none of the patient developed post-operative intra-ocular inflammation. Notably, patient 2 presented with per-operative subretinal and intra-vitreal hemorrhage at the first point of injection with very quick resorption of blood several days after surgery. Although he developed two patches of atrophy in this eye, those were concealed into the injections sites and did not progress at all, suggesting mechanical etiology for these atrophic areas more than an inflammatory origin. Finally, surgical technique may contribute to post-injection chorioretinal atrophy development. It has been demonstrated by Scruggs et al. that subretinal injection of retinal progenitor cells in Yucatan mini-piggs could trigger RPE pseudo geographic atrophy [12]. Modalities of injection (*i.e.,* pre-bleb formation, foot-pedal control for injection, localized ILM-peeling before injection) are other factors that may influence greatly the development of atrophy following VN injection as discussed in Gange et al. study [8]. In our study, surgery might have influenced the development of chorioretinal atrophy. In the two eyes remaining free of atrophy after 24 months, ILM peeling was performed at the injection site before VN subretinal injection. Those slight changes from the recommended injection protocol (which was used for the two first operated eyes which developed atrophy) might prevent RPE damage and possible subsequent pseudogeographic atrophy development, at least at the injection site. Indeed, once ILM is peeled, subretinal injection is easy and smooth, and there is no need to put pressure on the retina or the RPE to create retinal detachment. Fluid is penetrating the subretinal space even without penetrating the retina with the 42 Gauge cannula (See Video clip 1). VN injection was performed manually by the same assistant for all three patients after reducing intraocular pressure to 10 mmHg. Gange et al. reported the development of chorioretinal atrophy after foot-pedal control injection by the surgeon with limited maximum injection pressure of 16 PSI [8]. From our experience, injection pressure to obtain retinal detachment seems minimized when ILM has been peeled at the

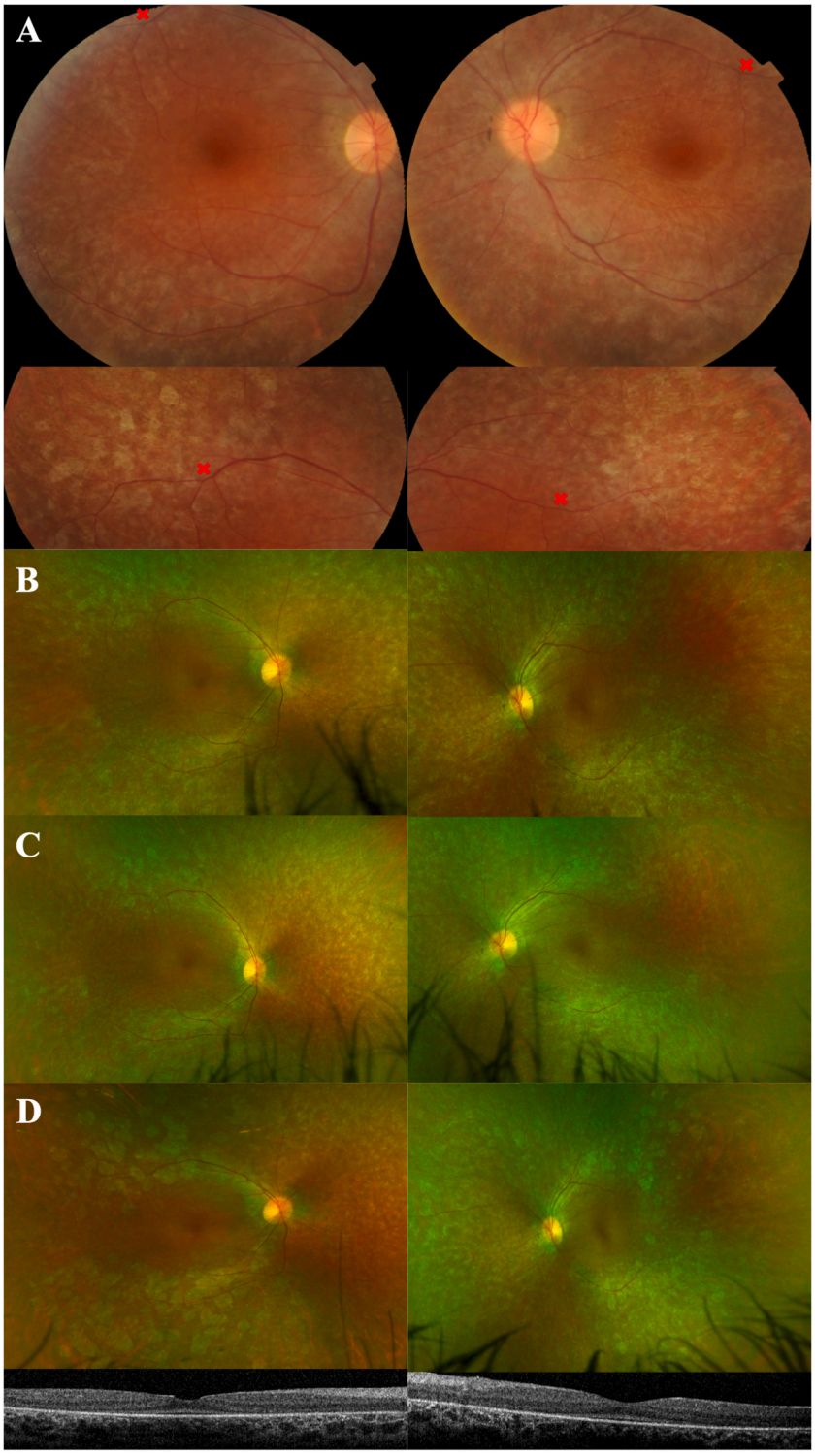

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Fig. 4. Pre- and post-operative non-mydriatic retinographies (NMR) and ultra-wide field fundus imaging (UWF) of both eyes of patient 3. Internal limiting membrane (ILM) peeling was performed at the injection site (red crosses) in both eyes. A. Pre-operative NMR showing bilateral nummular chorioretinal alterations in mid and extreme retinal periphery with no chorioretinal atrophy associated. Magnification on superotemporal mid retinal periphery below, showing nummular chorioretinal alterations and VN injection site (red crosses) more clearly. B. One month post-operative ultra-wide field fundus imaging (UWF) showing no chorioretinal atrophy development either at or around the injection site. C. Six months post-operative ultra-wide field fundus imaging (UWF) showing no chorioretinal atrophy at or around the injection site. D. Eighteen months post-operative UWF showing bilateral progression of the pre-operative nummular alterations toward multiple epithelial atrophic patches, while the injection site remains free of focal chorioretinal atrophy. Corresponding spectral-domain optical coherence tomography (SD-OCT) below showing global thinning of external retinal layers due to Leber congenital atrophy (LCA).

injection site. When ILM peeling is not performed, there is a high risk of small RPE traumatism with the 24 Gauge canula before injection, which could in some case expose choroidal blood circulation to VN product and probably increase the risk of immunologic reaction. This hypothesis could explain the rapid extension of macular atrophic scars from the injection site. Indeed, in many cases reported in the literature, the initial atrophic lesion is located at the injection site and then progresses towards the macular area [6–8]. We did not see this type of atrophy in our eyes treated with ILM peeling prior to VN injection. Thus, two different types of chorioretinal atrophy following VN treatment might exist. The first type, which is located at the injection site area, seems to be related to the injection technique and might be prevented or delayed by pre-injection ILM peeling. The second type seems to reflect photoreceptor rescue phenomenon after VN injection, while VN toxicity or LCA progression could also play a role.

The limitation of this study is related to the very small number of cases, which can reduce the applicability of the results. However, the unilateral development of atrophy, only in eyes with the non-modified injection technique, compared to contralateral unaffected eyes in which pre-injection ILM peeling was performed, is still an argument for an existing correlation between ILM peeling and focal chorioretinal atrophy development. Adding one surgical gesture, like ILM peeling, could be associated with an increased risk of operative complications [13] which, fortunately, was not the case in the present study but should be kept in mind for future practice.

5. Conclusion

In conclusion, ILM peeling before VN injection seems to be a smoother and safer technique to administer VN treatment and may protect the eye from secondary atrophy developing at the injection site. Another type of atrophy exists, which might not be related to the injection technique but more likely to VN effect and correlates with FST improvement. Further studies are needed to confirm the relation between the injection method and atrophy development.

Ethics statement

The patients' data were collected as part of the PERCEIVE study. PERCEIVE (Novartis) is an ongoing global registry-based post-authorization study designed to evaluate the real-world long-term safety profile of VN and to assess visual function over 5 years. This study was reviewed and approved by the "Comité de protection des personnes Sud-Méditerranée II" (ethics approval number: 219C31) and complies with all regulations. All patients provided informed consent or parental permission for the publication of their anonymized case details and images.

Data availability statement

Has data associated with your study been deposited into a publicly available repository?
No.
Sharing research data helps other researchers evaluate your findings, build on your work and to increase trust in your article. We encourage all our authors to make as much of their data publicly available as reasonably possible. Please note that your response to the following questions regarding the public data availability and the reasons for potentially not making data available will be available alongside your article upon publication.
Has data associated with your study been deposited into a publicly available repository?
Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Lea Dormegny: Writing – original draft, Software, Data curation. **Fouzia Studer:** Formal analysis, Data curation. **Arnaud Sauer:** Software, Methodology, Formal analysis. **Laurent Ballonzoli:** Software, Resources, Methodology. **Claude Speeg-Schatz:** Validation, Supervision. **Tristan Bourcier:** Validation, Supervision. **Helene Dollfus:** Validation, Resources, Funding acquisition. **David Gaucher:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

This study did not require any financial support.
The authors have no conflicts of interest to declare.

Acknowledgements/disclosures

This study did not require any financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25154.
The authors have no financial aid to disclose.

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