Corneal iatrogenicity of Belantamab Mafodotin (GSK2857916), Clinical and Morphological In Vivo Confocal Microscopy follow-up of a case series

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ARTICLE

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ABSTRACT

Objective : To highlight the potential importance of confocal microscopy (IVCM) in the follow-up of patients with refractory multiple myeloma treated with Belantamab Mafodotin.

Methods : A retrospective case series of 8 patients with refractory multiple myeloma treated with belantamab mafodotin was reported. Ophthalmologic follow-up of these patients every 3 weeks before each new infusion included systematic corneal examination with IVCM. A complementary analysis of the morphological data collected in IVCM was performed to evaluate the density, the average size and the circularity of the lesions observed.

Results : In case 1, the iatrogenic damage was maximal at the 6th week of follow-up with an important damage of Bowman's layer, leading to the suspension of the treatment. After resumption of treatment at a reduced dosage, the morphological damage to the cornea was reduced. In case 2, the onset of iatrogenic damage related to the treatment was observed but the follow-up was interrupted early because of therapeutic escape of the disease. In case 3, a prolonged follow-up could be performed showing a good tolerance to the treatment. In case 4, a decrease in visual acuity was observed at the 6th week of follow-up in connection with the treatment-related toxicity well observed in IVCM. Follow-up was then interrupted due to therapeutic escape of the disease. In cases 5 and 6, a significant decrease in visual acuity was observed at the 6th week in relation to iatrogenic morphological anomalies of the central cornea. The resumption of treatment at a reduced dosage was accompanied by an improved tolerance. In cases 7 and 8, the patients did not develop specific damage.

Conclusion : Our study showed the interest of corneal morphological follow-up in IVCM in patients treated with belantamab mafodotin in order to detect early signs of corneal iatrogenicity and to guide the management accordingly, before the suspension of treatment.

INTRODUCTION

Multiple myeloma (MM) is a malignant B-cell neoplasm characterized by uncontrolled and destructive clonal proliferation of plasma cells within the bone marrow (1). This is the second most common hematologic malignancy after lymphoma and it represents 1% of all cancers (2).

Advances have been made in the management of this pathology, with the emerging of novel therapies such as immunomodulators and proteasome inhibitors, but outcomes remain poor at the stage of relapse or refractory disease (3), reinforcing the need for therapies that could provide a response to the tumors that were resistant to other treatments until then.This problem is challenged by new targeted immunotherapies which could induce a deeper and more durable response than conventional treatments (4).

Belantamab Mafodotin (belamaf, GSK2857916, GSK, brentford, UK) is a targeted therapy from the group of Antibody-Drug Conjugates (ADCs) (5) They are composed in one hand of a humanized IgG1 monoclonal antibody (mAb) against the B-cell maturation antigen (BCMA) combined in the other hand with a tubulin polymerization inhibitor agent (Monomethyl Auristatin-F, MMAF) (6). BCMA, also called TNFRSF17, is part of the family of TNF receptors, essential for the plasma cells survival (5). It is ubiquitously expressed by malignant MM cells, but lacking on naive and memory B cells, making it a privileged therapeutic candidate (7,8).

Promising results in patients with relapsed/refractory multiple myeloma (RRMM) have been shown in the preclinical and clinical studies (9, 10). In France, a so-called « cohort » Temporary Authorization for Use (TAU) was granted on April 2020 followed by a Marketing Authorization valid in august 2020 for this immunoconjugate as monotherapy for the treatment of RRMM, in adults patients who have received at least three previous lines of treatment including one immunomodulatory agent (IMiD), one proteasome inhibitor (IP) and one anti-CD38 mAb, whose disease progressed during the last therapy (11).

Several adverse events could occur with the use of Belantamab Mafodotin, especially corneal iatrogenicity. They were reported in its clinical development (6,12). Morphological changes in the corneal epithelium were the most common adverse

event. In phase II study, they were observed at a frequency of up to 70% for a posology of 2,5mg/kg (13).

Therefore, the use of this new targeted therapy, requires a collaboration between ophthalmologists and haemato-oncologists for the monitoring of the treated patients (14,15).

In the field of exploring ocular surface diseases, IVCM imaging has a well-demonstrated interest : corneal dystrophies (19,20), infectious keratitis (21) and ocular surface tumors (22). Recently, our team reported the interest of monitoring the cornea with IVCM in early detection of ocular toxicity induced by Belantamab Mafodotin, rising the key role of IVCM in the whole therapeutic management (23).

The main objective of this study was to better define the morophological changes of the cornea for patients treated with belantamab mafodotin using IVCM. It should allow a better therapeutic management. The secondary objective was to better understand the mechanisms involved in the corneal toxicity of belamaf.

We report in this article, a prospective case series of 8 patients treated with belantamab mafodotin in the context of refractory MM. They were followed clinically regularly and we used In Vivo Confocal Microscopy (IVCM) to monitor the corneal iatrogenicity.

PATIENTS & METHODS

A prospective cohort of 8 patients affected by a MM and treated with belantamab mafodotin was consecutively enrolled. To be included in the study, the patients had to be treated for a MM, and to have been resistant to at least 3 previous lines of treatment induced by the hematology department who therefore indicated a therapy with belantamab mafodotin. The patient's ocular condition had to be suitable for the initiation of this treatment. We discussed on each and every case with the referring hematologist to better evaluate the balance between the ocular functional risk and the patient's vital prognosis.

Ophthalmological follow-up of each patient included a pre-therapeutic evaluation, then a consultation every three weeks before each new infusion of belantamab

mafodotin. Each pretherapeutic consultation included the collection of symptoms that had occurred since the previous treatment, a visual acuity measurement using the Monoyer scale then converted into a logMAR value (24), a slit-lamp clinical examination with photographs (Haag-Streit lamp, BQ 900), and a corneal morphological analysis using IVCM (Heidelberg Retina tomograph II, Rostock Cornea Modulus). The first pretherapeutic consultation also included an evaluation of the fundus after mydriatic dilatation and a macular examination by optical coherence tomography (OCT-SD, Spectralis Heidelberg), in order to rule out any other origin of reduced visual acuity.

A dose adjustment or a permanent interrruption was decided according to the recommendations suggested for the management of belantamab mafodotin. It depended of the occurrence of ocular adverse events (16,25).

We used Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 to assess and classify the symptoms reported during the medical questioning (26).

On the level of the clinical signs, the meibomian gland dysfunction (MGD) was evaluated by the staging of the international workshop on MGD (27) the superficial punctuate keratitis was graduated following Oxford classification (28). Corneal epithelial microcysts induced by the therapy were rated in peripheric or diffuse damage of the cornea according to their topographic arrangement.

IVCM was performed at the center and periphery of the cornea. An additional analysis, using the ImageJ software (NIH, USA), completed the exam, to research several parameters : the density per mm2, the average area in µm as well as the circularity index (between 0 and 1) of the lesions assessed. Small sizes hyperreflectivity's less than 10 µm were not taken into account in order to improve measurement quality.

These measurements were achieved layer by layer, from the superficial epithelium of the cornea to the Bowman layer (29).

RESULTS

The clinical and morphological ophthalmological follow-up as well as the images of the IVCM and the therapeutic adaptation decision at the end of each check-up are summarized in the Tables and Figures (Supplemental Data).

CASE 1

A 61-year old woman who must start belantamab mafodotin treatment was included. In her history, MM had been diagnosed in 2008 and her disease had already been refractory to 6 previous lines of treatment. The clinical and morphological IVCM follow-up of this patient are summarized in the table 1 (Supplemental Data)

First examination (Week 0 [W0]). The slit lamp examination found a superficial punctate keratopathy as well as a posterior blepharitis, with theoretical contraindication to the treatment. A reference imaging in IVCM was carried out, not finding any notable characteristics but keratitis The hematology department decided to initiate therapy with belantamab mafodotin because of the patient's vital prognosis and the absence of any other therapeutic alternative. Therefore, she received a first infusion of belantamab mafodotin at the posology of 180 mg corresponding to 100% of the theoretical dose (2,5mg/kg).

W3. The slit lamp examination found an early appearance of microcystic keratopathy only on the peripheral cornea without ulceration or visual impact. IVCM examination found discrete clusters of hyperreflective material mainly localized at the Bowman's layer and basal epithelium. These deposits only affected the peripheral cornea at this moment. Following this consultation, and given the reference consultation data, there was no ophthalmologic contraindication to continue the hematologic therapy.

W6. The slit lamp examination found an increase in superficial punctuate keratopathy, as well as microcystic epithelial keratopathy progressing centripetally. IVCM examination found a worsening of the corneal involvement with an increase in basal epithelium and Bowman's layer hyperreflective deposits, diffusely over the entire corneal surface, forming real « bunch of grapes » shaped clusters. Given the corneal iatrogenicity, we decided to taper off the treatment, and the patient did not receive third dose.

W9. Slit lamp we found microcystic keratopathy aspect even more dense, bilaterally (Figure 1).

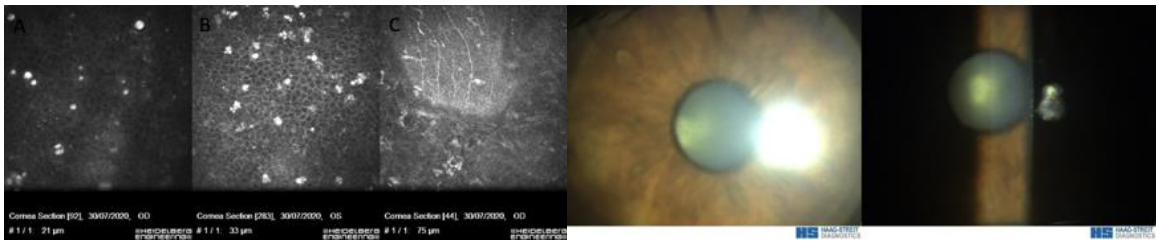


Figure 1. Case 1: IVCM at W9. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Slit lamp examination at W9: Aspect of diffuse microcystic epithelial keratopathy in both eyes. Images taken from the central cornea.

W12. IVCM found at the level of superficial epithelial layers the appearance of intraepithelial microcysts, still identifiable but less dense. At the level of basal epithelial layers, new deposits were noted in the peripheral cornea only. The Bowman's layer examination was relatively stable with few new active deposits either on the periphery or in the center of the cornea. 75% theoretical dose was administered.

W15. Clinical slit lamp appearance was stable. Using IVCM, there was at the central cornea an asymmetric increase in basal epithelial deposits, more important on the left eye. There was also an increase in the density of intraepithelial microcysts into superficial epithelium, giving on some images of hyperreflective « balloon release ». For the peripheral cornea, the analysis was similar to the previous consultation. The hematology department decided to stop treatment with belantamab mafodotin due to a therapeutic failure on RRMM.

5 months after last dose. Visual acuity had returned to baseline, as was theslit lamp examination with disappearance of the microcystic keratopathy. IVCM revealed a complete regression of all the lesions with a completely normal morphological evaluation of the cornea (Figure 2).

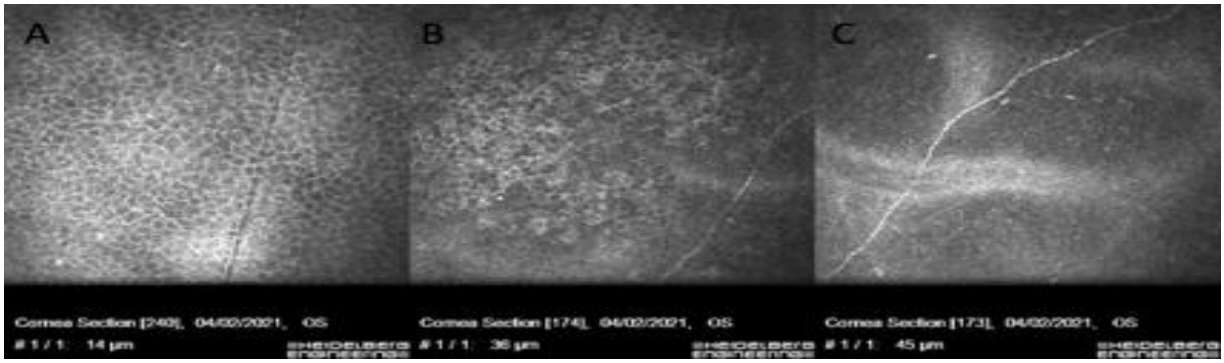
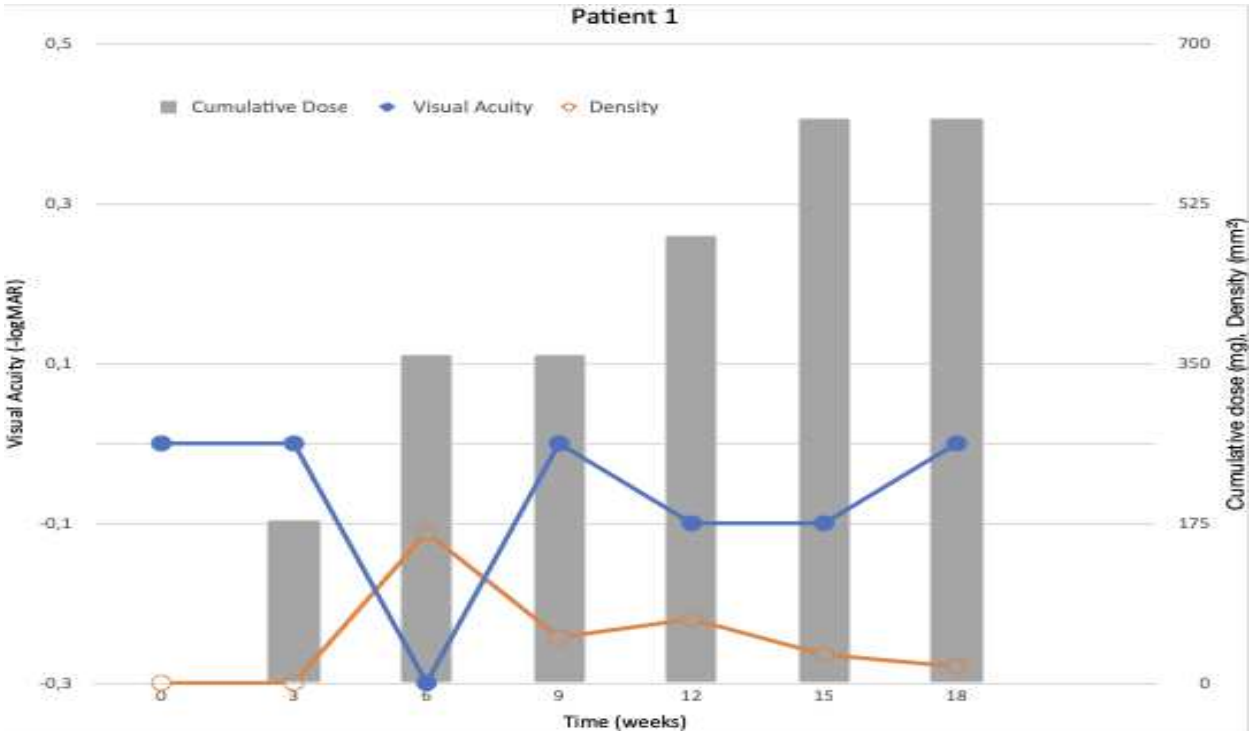


Figure 2. Case 1: IVCM 5 months after stopping treatment. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the central cornea. IVCM images at the level of Bowman layer testified the « wash-out » period in the treatment, showing absence of new lesions at this level. There was an increase of degenerative microcysts density within the superficial epithelium of the central cornea. At the end of this consultation, taking into consideration the improvement of the damage as imaged by IVCM, we recommended to start the treatment again, with a 75% dose (130mg).

This case illustrates that the dose of belantamab-mafodotin could be adjusted according to corneal IVCM imaging in order not to impair the corneal anatomy and function, as showed by the stability of corneal iatrogenicity at 75% dose together with the complete reversibility of the damage after final treatment stop.



Graph 1 : Following of Visual Acuity over time, according to the density of the deposits in the Bowman's layer, and the cumulative dose received by the patient 1.

CASE 2

In May 2020, we receive a 77-years-old man who must start treatment with belantamab mafodotin as 4th line of treatment for an RRMM. The clinical and morphological IVCM follow-up of this patient are summarized in the table 2 (Supplemental Data).

W0. During the pre-therapeutic consultation, he reported the presence of ocular secretions. The slit lamp clinical examination bilaterally found no patent abnormalities. A first reference examination in IVCM was carried out not finding any anomaly of the cornea epithelium. At the end of this consultation, we authorized the therapy with belantamab mafodotin. Thus, the patient received a first dose at 2.5mg/kg (170mg).

W3. In IVCM, there were minimal hyperreflective deposits in the basal epithelium and the Bowman's layer, but only within the paralimbic cornea area. At the end of this consultation, we issued a favorable opinion for the continuation of treatment. The patient received a second infusion of belantamab mafodotin at the dose of 190mg. The disease quickly turned out to be refractory to this therapy and the patient could

not be reassessed due to a deterioration in his general condition. It was decided in a multidisciplinary consultation meeting to stop therapy with belantamab mafodotin.

This case I) confirms the infraclinical deposits that begins at the periphery of the cornea and ii) shows the interindividual variability of the quickness of the clinical apparition in slit lamp of the iatrogenicity of Belantamab mafodotin.

CASE 3

In December 2020, we receive a 66-year-old man who must start treatment with belantamab mafodotin in 5th line in the management of a RRMM. Ophthalmologically, he presented severe amblyopia on the right eye since childhood, of inorganic origin. The clinical and morphological IVCM follow-up of this patient are summarized in the table 3 (Supplemental Data).

W0. The slit lamp examination was normal. Initial morphological analysis in IVCM was normal in both eyes. At the end of this consultation, we gave our agreement to the hematology department to start a belantamab mafodotin therapy. Therefore, the patient received a first dose at a dosage of 2.5mg/kg (i.e., 170mg).

W3. In IVCM, we mainly noted the appearance of a few very small hyperreflective deposits in the Bowman's layer, only at the peripheral cornea, bilaterally. Central cornea examination was normal. Thus, the patient received a second dose of belantamab mafodotin at 100% of the theoretical posology (i.e., 175mg).

W6. The slit lamp examination found an incipient modification, mainly paralimbic epithelial keratopathy (Figure 3).

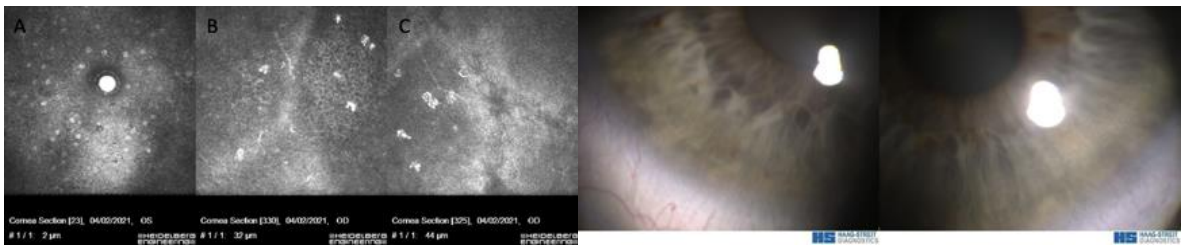


Figure 3. Case 3: IVCM at W6. (A): superficial epithelium of the left eye / (B): basal epithelium of the right eye / (C): Bowman layer of the right eye. Slit lamp examination at W6: Aspect of incipient paralimbic keratopathy in both eyes. Images taken from the peripheral cornea.

Morphological examination in IVCM showed an increase in hyperreflective deposits mainly in the paralimbic area. We informed the hematology department about this worsening of the morphological impairment, but the continuation of the therapy was authorized due to the absence of functional repercussions. Therefore, the patient received a new dose of belantamab mafodotin at 175 mg.

W8. The slit lamp examination was stable with an aspect of non-microcystic paralimbic epitheliopathy. IVCM examination showed increased deposits within the basal epithelium and the Bowman's layer. This increase in damage mainly concerned the peripheral cornea and to a lesser extent the central cornea, but not enough to affect the patient's visual acuity and quality of life. Therefore, the following week the patient received a 4th dose of belantamab mafodotin, at a dose of 175mg.

W12. Visual acuity and the slit lamp examination were stationary. The morphological analysis in IVCM was stable. At the end of this consultation, we had no contraindication to continue the treatment. Due to his general condition deterioration, the patient was not able to receive the next dose following our consultation. Belantamab mafodotin targeted therapy was suspended and resumed a couple of months after.

W22. We convened the patient 3 weeks after that the belantamab mafodotin therapy was resumed. Visual acuity was unchanged. Likewise, the slit-lamp examination still found this aspect of paralimbic epithelial keratopathy without microcyst. In IVCM, the analysis testified to the « wash out » period in patient care. The appearance being very similar to the first 2 follow-up consultations, with few hyperreflective deposits in the peripheral cornea, almost non-existent at the level of the central cornea. At the term of this consultation, we still had no contraindication to continue the treatment with belantamab mafodotin. Even so, patient management was discussed in a multidisciplinary consultation meeting and the therapy with belantamab mafodotin was definitively discontinued due to a therapeutic failure on RRMM.

2 months after last dose. A final consultation was performed 2 months after the last dose of belantamab mafodotin to ensure the reversibility of corneal iatrogenicity induced by this treatment. Visual acuity was unchanged. Slit lamp examination was stable, with even a decrease in the paralimbic epithelium granity aspect. IVCM

analysis found a complete regression of hyperreflective clusters associated with the therapy by belantamab mafodotin (Figure 4).

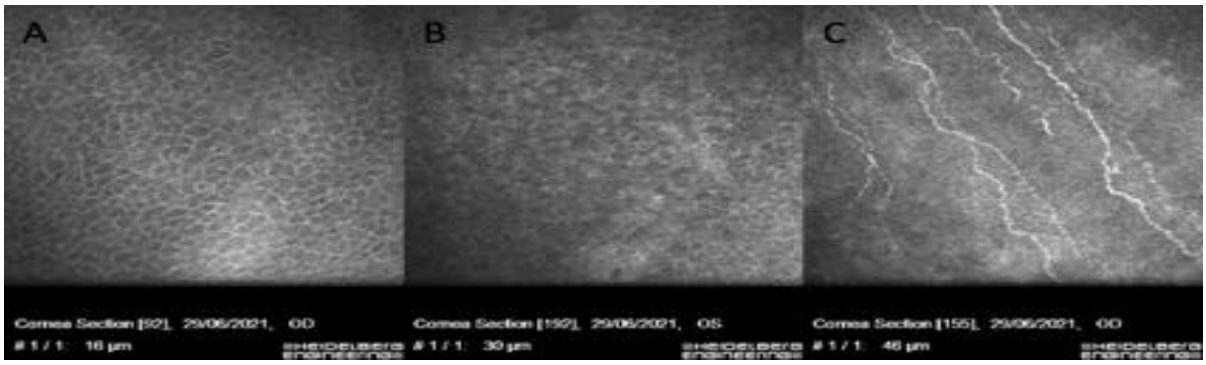


Figure 4. Case 3 : IVCM 2 months after last dose. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman's layer of the right eye. The analysis was normal and similar for the peripheral and central cornea.

This case is very relevant. It teaches the kinetic of the lesions, their provision and layout within the cornea. It also shows the interindividual variability in the severity of the deposits, and the clinical impact on the visual acuity and the symptoms. Eventually, it confirms the wash out period.

CASE 4

In January 2021, we receive a 70-year-old woman for a pre-therapeutic assessment before starting treatment with belantamab mafodotin as part of a stage III IgA kappa RRMM. It was the 5th line of treatment. The clinical and morphological follow-up in IVCM of this patient are summarized in the table 4. (Supplemental Data)

W0. The slit lamp examination found an aspect of palpebral malocclusion, responsible for a superficial punctuate keratitis. In IVCM, the initial morphological analysis of epithelial layers was unremarkable. On the other hand, at the level of the Bowman's layer, there was a rarefaction of the subepithelial nerves related to a chronic lagophthalmos. After consulting the hematology department, it was decided to initiate this therapy because of the potential life benefit which was greater than the theoretical functional risk. Therefore, the patient received a first dose of belantamab mafodotin at 100% of the theoretical dose.

W3. The clinical examination was improved by local treatments. Morphological analysis by IVCM found an onset of iatrogenic involvement exclusively in the basal

epithelial layers and the Bowman's layer of the peripheral cornea. The aspect of the central cornea was unchanged. Thus, the patient received a second dose of belantamab mafodotin at the same posology (155mg).

W5. There was a slight decrease in visual acuity. The slit lamp examination seemed to find an aspect of incipient microcystic keratopathy at the peripheral area of the cornea. In IVCM, the examination showed an aggravation of the ocular toxicity with damages of the superficial epithelial layers at the peripheral cornea including the appearance of some microcysts (Figure 5), but especially an extension of the iatrogenicity towards the central cornea, which was until then intact.

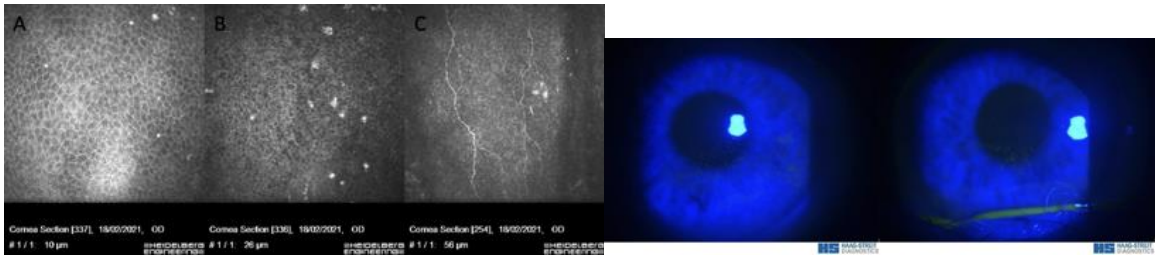


Figure 5. Case 4: IVCM at W5, peripheral cornea. (A): superficial epithelium of the left eye / (B): basal epithelium of the right eye / (C): Bowman layer of the right eye.

At this level we found hyperreflective clusters at the basal epithelial layers and poorly in the Bowman's layer. These changes were more important on the right eye (Figure 6).

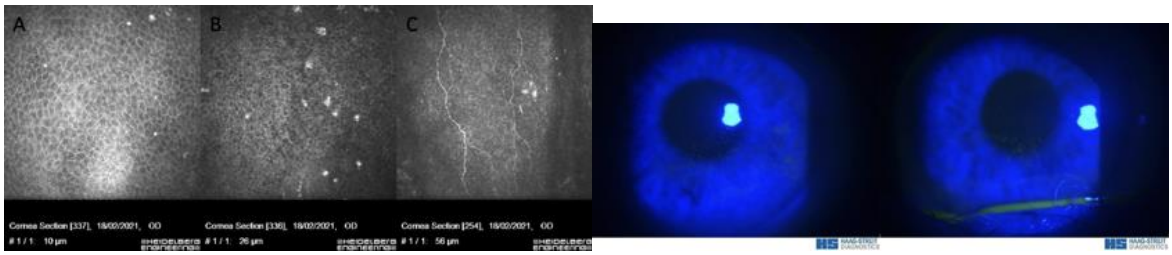


Figure 6. Case 4: IVCM at W5, central cornea. (A): superficial epithelium of the right eye / (B): basal epithelium of the right eye / (C): Bowman's layer of the right eye. Slit lamp examination at W5: Aspect of superficial punctuate keratopathy in both eyes in blue light.

At the end of this new ophthalmological assessment, due to the increased morphological impairment in IVCM but without significant impact on the patient's visual acuity, we authorized the continuation of treatment but with a recommendation

to reduce the posology at 75% of the theoretical dose. The hematology department informed us of their decision to stop the therapy by belantamab mafodotin due to a therapeutic failure on her RRMM.

6 weeks after last dose. There were no longer any detectable signs associated with belantamab mafodotin toxicity. The rest of the exam was unchanged. In IVCM, the morphological analysis found a clear regression of the anomalies considered to be active, mainly the basal epithelial layers and Bowman's layer deposits. At the level of the superficial epithelial layers, there were still some hyperreflective deposits, rather round in shape, which correspond to the final pathway of these toxic degenerative lesions whose kinetics follow the corneal epithelial renewal.

This case can allow us to formulate a hypothesis about the topography of the deposits that provokes a loss of visual acuity. Indeed, the IVCM shows deposits in the superficial layers of the center of the cornea, but the Bowman's layer remains almost intact. Visual acuity seems to depend on the amount of deposits within the Bowman's layer in the central area of the cornea.

CASE 5

In February 2021, we receive a 69-year-old woman for a pretherapeutic evaluation before starting therapy by belantamab mafodotin in the context of MM refractory to 4 previous lines of treatment. The clinical and morphological ophthalmological follow-up as well as the therapeutic adaptation decision at the end of each check-up are summarized in the Table 5 (Supplemental Data).

W0. During this first consultation, slit lamp examination found no pathological features besides a bilateral corticonuclear cataract responsible for her moderate visual acuity. The initial morphological evaluation in IVCM confirmed the normal character of the corneal epithelium as well as well as the Bowman's layer. Following this first evaluation, she received a first dose at 100% of the theoretical dose.

W3. The slit lamp examination found an aspect of incipient paralimbic microcystic keratopathy. In IVCM, there was mainly toxic damage to the peripheral cornea with the presence of irregularly shaped hyperreflective clusters within the basal epithelium and the Bowman's layer. Also, the superficial epithelium already had hyperreflective deposits, but less dense and rounder in shape. The central cornea

did not show any significant sign of iatrogenicity at this moment, except for a few very small deposits in the Bowman's layer. Due to the absence of functional impact, the patient received a second dose of belantamab mafodotin at the same posology (162.5mg).

W6. This time, the ophthalmologic functional signs were present and dominated by eye burns sensations, photophobia, and a blurred vision. Visual acuity was significantly decreased on the left eye. Slit lamp examination was marked by an increase in the appearance of the microcystic keratopathy, now which was diffuse throughout the corneal area. Corneal morphological analysis in IVCM found an increase in the density of the lesions previously described in the peripheral cornea, there was also the presence of microcyst within the superficial epithelium. Examination of the central cornea, which until then had been almost intact, now showed numerous hyperreflective deposits involving all epithelial layers (Figure 7).

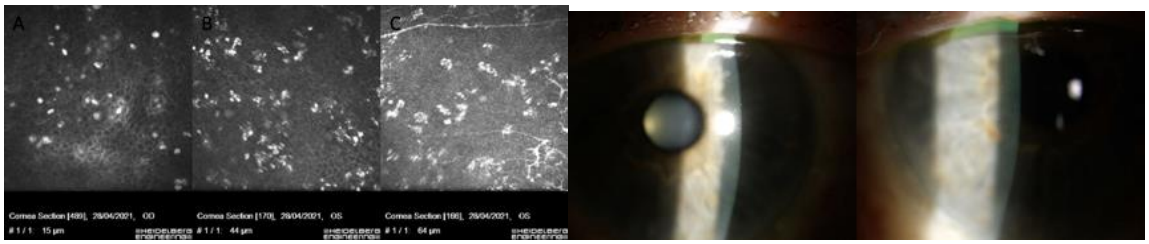


Figure 7. Case 5: IVCM at W6. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman's layer of the left eye. Slit lamp examination at W6: Aspect of diffuse microcystic epithelial keratopathy in both eyes. Images taken from the central cornea.

At the end of this consultation, we recommended the suspension of treatment. Therefore, she did not receive a new dose and we reassessed the situation 3 weeks later.

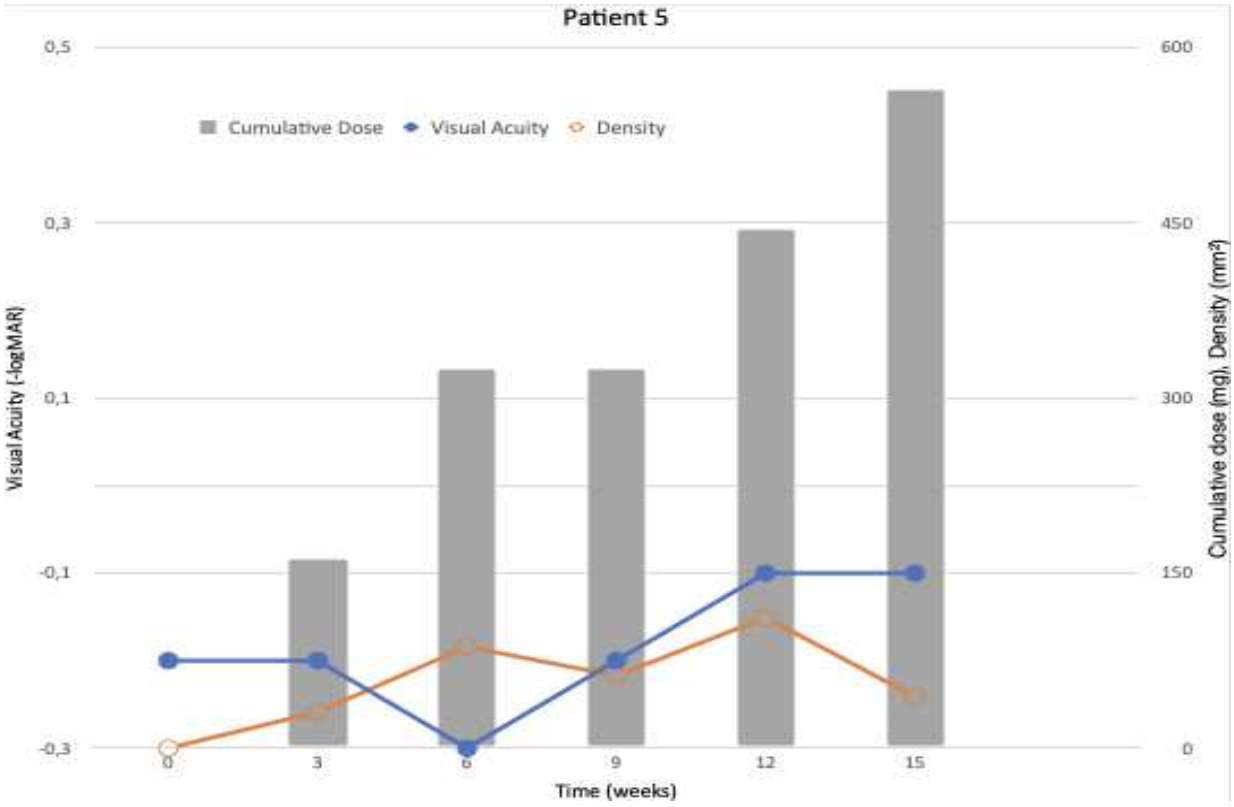
W9. The patient attested an improvement in her symptoms with less photophobia and less blurred vision. Visual acuity had recovered well. The slit lamp examination found a migration of microcystic keratopathy appearance affecting only the central and paracentral areas of the cornea. In IVCM, there was an overall decrease in deposits on all epithelial layers and Bowman layer, both in the center and the periphery of the cornea. Although superficial microcysts persisted in the center of the

cornea, this did not affect the patient's visual acuity (Figure 9). Given the improvement in visual acuity and morphological appearance in IVCM, we authorized the resumption of therapy with belantamab mafodotin at 75% of the theoretical dose. Thus, in agreement with the hematology department, the patient received a new dose at 120mg.

W12. During this consultation, she reported blurred vision again on the left eye but without significant impact on her daily activities. She still presented a slight photophobia. Visual acuity was stable on the right eye. Concerning the left eye, it was moderately reduced compared to the previous consultation. On slit lamp, we still found the appearance of a diffuse microcystic keratopathy. IVCM analysis showed an increase in hyperreflective deposits at the central cornea, in particular within basal epithelium and the Bowman's layer, more importantly on the left eye, which was still a times consistent with the patient 's visual acuity. At the peripheral cornea, an increase in the density of lesions was also noted. At the end of this new evaluation, we gave our agreement for the continuation of the therapy but still at the dosage corresponding to 75% of the theoretical dose. The patient received a further dose of belantamab mafodotin at 120mg.

W15. The patient had indeed received a new dose of belantamab mafodotin following our previous evaluation, however the patient's situation was discussed again during a multidisciplinary consultation meeting ten days later. It was decided to stop this therapy because of a therapeutic failure of her MM. The conclusion of this meeting was to be able to offer palliative care for this patient. We still maintained our consultation scheduled to follow the regression of corneal iatrogenicity. The slit lamp examination was generally stable. In IVCM, surprisingly we observed a decrease in the toxic deposits density, both in the center and the periphery of the cornea. This probably indicates a dose-dependent effect in this patient with a lower iatrogenicity induced at 75% of the theoretical dose.

This case teaches us the efficacity of the recovery of the symptoms when the treatment by Belantamaf Mafodotin is stopped and the short time necessary before release of the symptomatology. These features are very interesting in the management of the treatment for these patients with a severe pathology with a necessity of fast adaptation of posology to fight against the disease.



Graph 2 : Following of Visual Acuity over time, according to the density of the Bowman's layer deposits, and the cumulative dose received by the patient 5.

CASE 6

In June 2021, we received a 74-year-old man for a pre-therapeutic evaluation before starting therapy by belantamab mafodotin in the context of MM refractory to 5 previous lines of treatment. The clinical and morphological ophthalmological follow-up as well as the therapeutic adaptation decision at the end of each check-up are summarized in the Table 6 (Supplemental Data).

W0. The slit lamp examination found an epithelial dystrophy of granular appearance predominantly in the periphery. The initial morphological evaluation in IVCM showed a pre-existing sub-epithelial dystrophy, with hyperreflective deposits, more present in periphery. That IVCM observation raised a problem for us : how will we be able to distinguish the deposits caused by belamaf from those caused by his corneal dystrophy. Still, we decided to include him in our study and did all the density measures and calculations in the central area of the cornea. We agreed to start therapy with belantamab mafodotin, considering the absence of contraindication in

this patient. Thus, he received a first dose at 100% of the theoretical dose, i.e. 140 mg.

W3. The slit lamp examination also found a stable aspect. In IVCM, there was a beginning of toxicity mainly in the peripheral cornea, with the presence of hyperreflectivity clusters within the basal epithelium and the Bowman's layer. The superficial epithelium already had hyperreflective deposits. The central cornea did not show any significant sign of iatrogenicity at this moment, except for the already known deposits in relation to his granular dystrophy. Due to the risk of functional impact, we advised to reduce the posology at 75% for the second dose of belantamab mafodotin. Given the vital stakes of this treatment, the patient nevertheless benefited from a full dose of 2,5 mg/kg (140 mg).

W6. This time, the patient complains about a moderate loss of vision but didn't feel pain or eye burns. The slit lamp examination showed an important Superficial Punctuate Keratitis (oxford 4) and a diffuse epithelial microcystic keratopathy. Corneal morphological analysis in IVCM found an increase in the density of the lesions previously described in the peripheral cornea, there was also the presence of microcyst within the superficial epithelium. Examination of the central cornea now showed numerous hyperreflective deposits involving all epithelial layers. In order to quickly improve our patient's vision, we notified to our hematologists colleagues to lower the next dose of treatment. The patient received 1,92 mg/kg of belantamab mafodotin.

W9. The patient attested an improvement in his symptoms in the left eye : less blurred vision, but was still annoyed about the right one. The slit lamp examination still showed a Superficial Punctuate Keratitis stage 4 on the Oxford scale and a diffuse microcystic keratopathy. In IVCM, there was an overall stability of the deposits in all layers. Superficial microcysts persisted in the center of the cornea, but it's hard to identify precisely which one of the dryness or the iatrogeny is responsible of the blurry vision of the right eye. About the MM evolution, a change in the cure was decided, relying on the limited efficacity of the Belamaf and the side effects, ocular in priority.

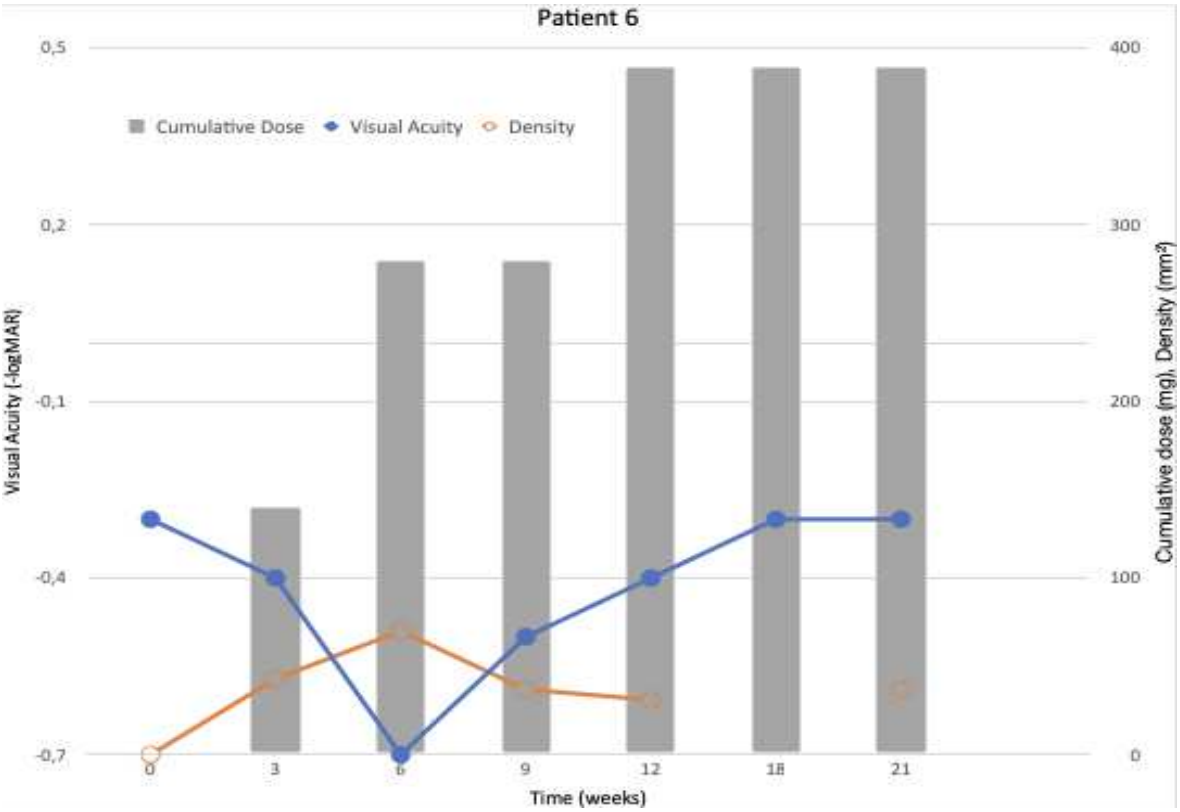
W12. The patient had stopped the Belamaf since 6 weeks when we got to see him again to check on his ophtalmological condition. The visual acuity struggles to

recover. About the slit lamp examination, we could observe an important regression of the subepithelial microcysts on both eyes. In IVCM, we saw a persistance of the diffuse subepithelial microcysts and hyperreflective deposits in each layer of the central cornea and of the periphery of cornea, although the patient didn't get the treatment for 6 weeks.

W18. The patient felt a great improvement of his symptomatology. His visual acuity was identical as the pretherapeutic exam. The slit lamp examination showed a spectacular improvement of his surface, with the complete disparition of the SPK thanks to a great therapeutic compliance from our patient that cured the dry syndrome, and a clear decrease of the microcysts. Unfortunately, that day, the IVCM was not usable because of some network connection problem.

W22. Slit lamp exam couldn't show any cysts, nore SPK. IVCM confirmed that all the specific deposits in relation with the belantamab mafodotin had disappeared. We could note that small round hyperreflective deposits in favor of inflammation can be individualized in the different layers.

This case can allow us to assume that the disappearing of the deposits follow the reverse order than the appearance one.



Graph 3 : Following of Visual Acuity over time, according to the density of the Bowman's layer deposits, and the cumulative dose received by the patient 6.

CASE 7

In June 2021, we received a 65-year-old man for a pre-therapeutic evaluation before starting therapy of belantamab mafodotin because the five previous cures did not prevent the worsening of his MM. The clinical and morphological follow-up in IVCM of this patient are summarized in the table 7 (Supplemental Data).

W0. Slit lamp examination of anterior segment of both eyes, intra ocular pressure, fundus, and IVCM were all within norms. Therefore, there was no contraindication to start Belamaf at the posology of 2,5 mg/kg.

W3. Symptomatology was still none. Examination wasn't modified. Besides, all additional exams were stable, especially the MCIV which was superimposable. We authorized the delivery of a new full posology cure of treatment (2,5 mg/kg).

W6. Visual acuity remained stable. The clinical slip lamp examination was the same. MCIV did not show any sign of iatrogenicity of the treatment. We gave our approvement to continue the treatment at the same posology but because of biological worsening, it was decided to switch the treatment. We organized a control consultation, but patient's general condition has deteriorated and the patient was weakened.

This case is the first one of our series in which we couldn't find any damage in IVCM after 2 first full doses of treatment and 6 weeks of follow-up.

CASE 8

In June 2021, we received in pre-therapeutic consultation a 74-year-old man.

He was a candidate to move to a 6th line treatment for his RRMM. The clinical and morphological follow-up in IVCM of this patient are summarized in the table 8 (Supplemental Data)

W0. The slit lamp examination did not find any pathological abnomalies, besides corticonuclear cataract and a blepharitis. We practiced a first IVCM that did not find

any specific irregularities. That's why at the end of our first consultation, we agreed to a 2,5 mg/kg introduction of belantamab mafodotin.

W3. The slit lamp examination was identical, as well as IVCM, that did not show any corneal iatrogenic toxicity. We gave our agreement to a new 2,5 mg/kg dose of treatment. Unfortunately, related to the deep worsening of general condition and according to the patients's wishes, palliative care was decided.

In this case, the patient didn't develop a keratitis three weeks after a single full dose of treatment which is common, the lesions appearing usually after several injections and around the sixth week.

DISCUSSION

Clinical examination versus IVCM.

Belantamab-Mafodotin is a targeted therapy available in the treatment of RRMM (11). Although full of promises, it has shown frequent corneal side effects in the preclinical and clinical studies (6,9,10), emphasizing the need for close collaboration between hematologists and ophthalmologists for using this new treatment.

This original prospective case series provides the first morphological follow-up of corneal damage related to this therapy using IVCM.

The corneal evaluation by IVCM at each visit makes it possible to show a particular tropism to the Bowman's layer. The evolution of corneal involvement over time revealed a migration of deposits to the outermost epithelial layers and to the center of the cornea, with rapid formation of intraepithelial microcysts also.

Microcystic keratopathy is a well-known side effect of ADCs using MMAF or a related molecule (17,30,31). Besides, visual acuity and microcystic keratopathy are the two main clinical endpoints taken into account during the follow-up in the dosage management recommendations for belantamab-mafodotin (16,25). Studies about the toxicity of ADCs suggest that microcystic keratopathy is responsible for blurred vision. (32,12,16)

However, our data show, for the first time, that corneal damage induced by belantamab mafodotin i) is not limited only to the corneal epithelium, and ii) also affects the Bowman's layer, which seems to be the most predictive factor for visual acuity decline. Indeed, in the most affected patients, the maximum of hyperreflective deposits in IVCM was obtained after 6 weeks of treatment initiation with, at this stage, diffuse lesions of the entire epithelium and Bowman's layer, associated with significant decrease in visual acuity. In the event of treatment suspension followed by a « wash-out » period, we observed a rapid regression of the deposits at the level of Bowman's layer associated with visual recovery although microcystic keratopathy persisted in the central cornea (case 1 and case 5).

Moreover, the clinical slit lamp analysis of microcystic keratopathy, is still subjective and not well correlated with what is found by IVCM. Thus, IVCM clearly appears to be a more accurate, quantitative and objective examination for monitoring the treatment's toxicity compared to clinical examination.

New pathophysiologal data provided by IVCM.

Main symptomatology in our case series was fluctuation in the visual acuity. This was found for 22% of cases in clinical development studies (39). Finally, the functional signs of dry eye were not very present in our patients, and that is consistent with clinical development studies in which symptomatology of dry eye was only found in 14% of cases (32). Such a visual acuity fluctuation is undoubtedly linked with the evolution of corneal toxicity over time, and notably underpinned by the optical aberrations generated by deposits within Bowman's layer and basal epithelium. On the contrary, we believe that epithelial microcyst may not really affect the visual acuity.

The exact mechanism behind this corneal iatrogenicity is still unknown. However, several hypotheses have been proposed in the ocular toxicity of ADCs associated with MMAF or another related molecule. The first would be a direct toxicity by binding to a basal epithelial corneal cell antigen, which is said to be similar to the ADC's target antigen (33). BCMA is not an antigen known to be present in the basal cells of the corneal epithelium, but we could assume the existence of another phenotypically similar antigen on which belantamab mafodotin could bind and exert direct toxicity. The second hypothesis put forward to explain these corneal side

effects would result in a non-specific absorption of ADC within the proliferating limbic stem cells, further leading to an alteration of mitotic processes. (16,17,33). Then, the normal renewal of corneal epithelium would allow the lesions to regress after tapering of the treatment (34). The lastest point could explain the kinetics observed in the location of morphological anomalies found by IVCM : first attack of the basal layers then of the superficial layers, as well as the centripetal evolution. Finally, to explain the damage on the Bowman's layer, a passive diffusion of the active molecule once internalized within basal epithelium layers is hypothesized (17,33). This mechanism could explain the presence of deposits at the level of the Bowman's layer but also the possible involvement of subepithelial nerves and anterior stroma. Whatever the exact mechanisms, it seems very likely that BCMA receptor or a related one is expressed by limbal stem cells of the cornea. These have indeed a hematopoietic origin as evidenced by the corneal epithelium renewal made up of cells from donors in bone marrow transplant patients, as well as the GVH disease that can occur in these patients (34,35).

Parrozzani and al. reported the presence of corneal nerve fragmentation as well as keratocyte activation within anterior stroma in some patients (33) treated with another ADCs associated with mafodotin. In our study, we also observed a tendency to corneal nerve fragmentation, but this modification is difficult to be accurately followed. This fragmentation is to be compared with the deposits observed at the Bowman's layer and, in all cases, is temporary like the rest of the corneal anomalies. On the other hand, keratocyte activation within anterior stroma was not found in our study. Therefore, if it could exist in other cases, it does not seem to have a major impact in the reduction of visual acuity linked to belantamab mafodotin therapy.

Whatever the severity, this corneal iatrogenicity results from a purely toxic phenomenon and the use of corticosteroid eye drops has proven to be ineffective and not necessary prophylaxis (36,13). Only the use of artificial tears or other agents promoting corneal healing should be used to limit functional symptoms. Decreasing or even suspending therapy are only recommended to manage these corneal events. The patient is also advised to apply a cooling eye mask during administration of belantamab mafodotin and in the hours following the infusion, which could in theory reduce the amount of drug reaching the cornea locally, although this has not been clinically demonstrated.

Interindividual variability of belamaf-related ocular damage as assessed by IVCM. There is also an inter-individual variability since not all patients presented modification of the Bowman's layer and/or corneal epithelium in the central cornea. For some, the morphological abnormalities detected by IVCM remained localized in the peripheral cornea without any impact on the visual acuity and quality of life, although there were clinically epithelial damages revealed by the slit lamp examination (case 3). This reinforces the value of morphological monitoring in IVCM compared to clinical monitoring alone.

Treatment suspensions or even discontinuations carried out for some patients allowed to observe in IVCM a rapid clearance of the Bowman's layer lesions, estimated at less than 6 weeks for most of our patients. The disappearance of anomalies in the most superficial layers was for its longer time, difficult to assess with accuracy in our case series due to resumption of treatment after suspension or to permanent interruption due to general therapeutic failure. Probably, this seems to have a delay of more than 9 weeks concerning epithelial microcysts and the most superficial deposits. At all events, examinations carried out long after time stopping treatment revealed a trend towards ad-integrum restoration of the corneal epithelium and the Bowman's layer in IVCM, testifying to the reversibility of this iatrogenicity. Thus, corneal epithelial recovery took place at the peripheral cornea first, and then at the central cornea, with a variable delay depending on each case.

Anyway, the ocular functional prognosis of this iatrogenicity must be evaluated in balance with the general repercussions of RRMM, as evidenced by the frequent therapeutic failures during the management of these patients (case 2 and case 4) whose short and medium-term survival remain low according to the most recent studies (37,2).

IVCM for adapting the dose.

Then, we observed that corneal damage especially at the Bowman level was recovering after a suspension period followed by resumption of cures at 75% of the theoretical dose (case 1 and case 5), in particular with the absence of new deposits in the Bowman's layer and the stabilization of visual acuity. IVCM provides an objective proof of dose-dependent effect, and may be crucial for determining a threshold dose that may not be exceeded.

As a result, the presence of specific hyperreflective clusters at the level of Bowman's layer would be predictive of a future decrease in visual acuity, independently of corneal epithelial damage.

Therefore, monitoring the Bowman's layer involvement in IVCM appears to be interesting for the management of patients treated with belantamab-mafodotin in order to reduce treatment dosage before the occurrence of a reduction in visual acuity.

In our cases series, we carried out a complementary analysis of the anomalies observed at the level of central cornea in order to measure their density, their average size and their circularity, considering that those are the central cornea modifications which have a real impact on visual acuity and patient quality of life. This showed that when density and average size of deposits in central cornea were important at the level of basal epithelial layers and especially of the Bowman's layer, the visual acuity decreased. We could hypothesize that a certain level of peripheral deep deposits may announce severe corneal damage that may lead after to treatment discontinuation. As a result, the deep peripheral density of belamaf-induced hyperreflective deposits as assessed by IVCM could be a putative marker for tapering off the treatment before major ocular issue, in order to prevent discontinuation. Circularity analysis testified to the irregular character of the deposits, forming « bunch of grapes » shaped clusters within the basal epithelial and the Bowman's layer, while those in the superficial layers had a rounder shape resembling microcysts.

Limitations of the present study.

However, a limitation of this study is the low number of patients with central involvement which does not yet allow the establishment of statistical criteria to guide management according to the extent of morphological involvement in IVCM. Another limitation of our study is related to the patient's systemic condition with MM : a significant proportion of our patients had interrupted follow-up due to progressive disease. This makes it difficult to obtain a precise definition of a median time to resolution of anomalies due to the low number of patients who can continue follow-up after treatment discontinuation for therapeutic failure.

Other Studies with a larger number of patients treated with belantamab mafodotin could be interest to support all our hypotheses. For example, we could seek “threshold density” of deposits at the Bowman’s layer, beyond which this impairment is accompanied by a significant reduction in visual acuity, in order to allow more precise and early management of this therapy before the loss of vision and the suspension of treatment.

CONCLUSION

In conclusion, the therapeutic arsenal available in the fight against RRMM could rely on belantamab mafodotin, a targeted therapy. It presents a demonstrated corneal iatrogenicity that could be avoided by a close communication between hematologist and ophthalmologist during the follow-up. The exact mechanism behind this iatrogenicity remains unknown but could probably be related to the presence of a BCMA-like receptor in corneal limbal stem cells on which belantamab mafodotin could be attached to exert direct toxicity.

IVCM made it possible to morphologically describe this corneal iatrogenicity with originally reported specific damage to the Bowman’s layer, then an evolution towards the formation of intraepithelial microcysts.

We could observe a dose-dependent effect and a threshold dose in this toxicity. Indeed, the corneal morphological impact was greater at 100% of the theoretical dose than 75%. Moreover, the layer of the cornea that seems to be responsible for the decrease of visual acuity has been identified as the Bowman’s layer, over than intraepithelial microcysts.

This study highlights the crucial benefits of non-invasive corneal morphological monitoring using IVCM in these patients, in order to i) allow early detection of belantamab mafodotin-induced corneal damage, and ii) guide management accordingly i.e. before the occurrence of a decrease in visual acuity. As a result, systematic ocular watch using IVCM may lead to dose adaptation before visual symptoms, further avoiding a treatment suspension that impairs vital prognosis.

Other studies with a larger number of patients are needed to prospectively use the data provided by IVCM and adapt the dose accordingly.

Declarations

Ethical Approval

Informed written consent was obtained from each enrolled patient in the trial.

Competing interests

All the authors declare to have no competing interests

Authors' contributions

Dr David Mostrel & Dr Kevin Marquant co-1st authors, Pr Denoyer 1st reviewer, Pr Arndt and Dr Quinquenel reviewers

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Availability of data and materials

All the data come from the internal ophtalmological software used in the Robert Debré Hospital, Reims and the Internal patient record available to all physicians in charge.

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Supplemental data

Tables

Table 1. Case 1: Follow-up of the symptoms and corneal changes as assessed by slit-lamp and in vivo confocal microscopy according to the therapeutic management.
(Right eye / left eye)

	Week 0	Week 3	Week 6	Week 9	Week 12	Week 15	5 Months after last dose
Symptoms (CTCAE score)							
Blurred vision (0-4)	NA	0 / 0	2 / 3	0 / 0	1 / 1	0 / 1	0 / 0
Photophobia (0-4)	NA	0 / 1	1 / 2	0 / 0	0 / 0	0 / 0	0 / 0
Clinical examination							
Superficial punctuate keratopathy (Oxf)	1 / 2	0 / 1	2 / 3	1 / 2	1 / 2	1 / 2	0 / 0
intraepithelial microcysts (n, p or d)	NA	p / p	d / d	d / d	d / d	d / d	n / n
Central cornea in vivo confocal microscopy							
Epithelial microcysts							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	12.5/ 6.3 14.9/ 14.3 0.76/ 0.90	25/12 .5 13.1/ 14.7 0.90/ 0.94	6.3/6. 3 14.6/ 14.7 0.86/ 0.94	12.5/62.5 14.5/15.7 0.90/0.84	0/0 0/0 NA
Superficial epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	18.8/ 87.5 9.1/7. 5 0.67/ 0.69	62.5/ 81.3 7.7/9. 1 0.74/ 0.80	56.3/ 62.3 9.2/7. 4 0.68/ 0.65	37.8/106 7.3/9.0 0.81/0.83	0/0 0/0 NA
Basal epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	87.5/ 219 8.6/8. 9 0.62/ 0.64	113/1 19 8.7/9. 1 0.70/ 0.75	43.8/ 93.8 8.7/7. 2 0.71/ 0.59	50/206 8.1/9.2 0.69/0.74	25/0 7.2/0 0.77/NA
Subbasal nerve plexus's layer hyperreflective deposits							

Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	163/169 7.1/8.9 0.62/0.64	50/50 6.6/6.3 0.56/0.64	18.8/68.8 7.6/6.4 0.64/0.72	31.3/31.3 6.9/7.9 0.55/0.59	31.3/18.8 6.6/10.6 0.60/0.56
Peripheral cornea in vivo confocal microscopy							
Epithelial microcysts							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	81.5/25 15.2/10.7 0.74/0.67	0/6.3 0/18.4 NA/0.88	0/0 0/0 NA	0/62.5 0/18.8 NA/0.77	0/0 0/0 NA
Superficial epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	12.5/31.3 6.9/8.5 0.84/0.72	150/138 8.4/6.8 0.60/0.67	87.5/62.5 8.0/7.1 0.74/0.72	31.3/56.3 6.0/7.6 0.53/0.62	6.3/62.5 7.4/8.8 0.74/0.81	0/0 0/0 NA
Basal epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	37.5/68.8 9.5/9.0 0.48/0.56	200/381 10.9/9.9 0.63/0.61	106/343 8.8/6.9 0.68/0.75	231/131 7.9/8.6 0.72/0.63	175/93.8 9.9/8.7 0.63/0.67	25/0 7.3/0 0.66/NA
Subbasal nerve plexus's layer hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	31.3/100 7.9/6.4 0.66/0.66	125/225 10.2/8.2 0.60/0.61	25/62.5 6.7/8.0 0.63/0.48	18.8/37.5 7.6/7.5 0.64/0.64	75/31.3 7.2/6.6 0.57/0.69	25/0 7.4/0 0.55/NA
Visual acuity, (logMAR)	0/+0.1	0/0	+0.1/+0.3	0/0	+0.1/+0.1	+0.1/+0.2	0/0
Delivered belamaf (3 weeks before, mg)	NA	180	180	0	130	130	NA
NA: not applicable; CTCAE: Common Terminology Criteria for Adverse Events; Oxf, Oxford score; n, p or d: none, peripheral or diffuse.							

Table 2. Case 2: Follow-up of the symptoms and corneal changes as assessed by slit-lamp and in vivo confocal microscopy according to the therapeutic management.
(Right eye / left eye)

	Week 0	Week 3
Symptoms (CTCAE score)		
Blurred vision (0-4)	NA	0 / 0

Photophobia (0-4)	NA	0 / 0
Clinical examination		
Superficial punctuate keratopathy (Oxf)	1 / 1	1 / 1
intraepithelial microcysts (n, p or d)	NA	n / n
Central cornea in vivo confocal microscopy		
Epithelial microcysts		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Superficial epithelial hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Basal epithelial hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Subbasal nerve plexus's layer hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Peripheral cornea in vivo confocal microscopy		
Epithelial microcysts		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Superficial epithelial hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Basal epithelial hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	12.5/12.5 6.9/6.2 0.64/0.65
Subbasal nerve plexus's layer hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	6.3/0 5.7/0 0.49/NA
Visual acuity, (logMAR)	0/0	0/0
Delivered belamaf (3 weeks before, mg)	NA	170
NA: not applicable; CTCAE: Common Terminology Criteria for Adverse Events; Oxf, Oxford score; n, p or d: none, peripheral or diffuse.		

Table 3. Case 3: Follow-up of the symptoms and corneal changes as assessed by slit-lamp and in vivo confocal microscopy according to the therapeutic management.
(Right eye / left eye)

	Week 0	Week 3	Week 6	Week 8	Week 12	Week 22	2 Months after last dose
Symptoms (CTCAE score)							
Blurred vision (0-4)	NA	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Photophobia (0-4)	NA	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Clinical examination							
Superficial punctuate keratopathy (Oxf)	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
intraepithelial microcysts (n, p or d)	NA	n / n	p / p	p / p	p / p	n / n	n / n
Central cornea in vivo confocal microscopy							
Epithelial microcysts							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	0/0 0/0 NA	0/0 0/0 NA	0/0 0/0 NA	0/0 0/0 NA	0/0 0/0 NA
Superficial epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	0/0 0/0 NA	0/25 0/7.2 NA/0.70	6.3/0 14.8/0 0.67/NA	0/0 0/0 NA	0/0 0/0 NA
Basal epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	6.3/0 6.6/0 0.79/NA	43.8/31.3 6.4/8.7 0.73/0.60	18.8/0 5.5/0 0.62/NA	6.3/0 6.3/0 0.87/NA	0/0 0/0 NA
Subbasal nerve plexus's layer hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	37.5/18.8 6.4/6.9 0.57/0.47	50/62.5 5.8/7.0 0.61/0.46	43.8/12.5 7.4/7.3 0.54/0.54	0/25 0/6.4 NA/0.44	0/0 0/0 NA
Peripheral cornea in vivo confocal microscopy							
Epithelial microcysts							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	0/6.3 0/18.9 NA/0.9	0/0 0/0 NA	0/0 0/0 NA	0/0 0/0 NA	

			3				
Superficial epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	31.3/25 12.2/6.1 0.66/0.61	0/87.5 0/11.9 NA/0.60	6.3/0 11.1/0 0.54/NA	6.3/0 5.5/0 0.89/NA	
Basal epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	87.5/50 11.1/7.1 0.41/0.69	68.8/125 11.7/10.2 0.59/0.62	31.3/75 8.6/6.2 0.67/0.79	37.5/31.3 6.3/6.6 0.81/0.78	
Subbasal nerve plexus's layer hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	81.3/31.3 10.5/6.4 0.54/0.59	143.8/56.3 9.8/7.9 0.45/0.62	37.5/31.3 7.6/7.1 0.50/0.44	25/37.5 7.2/5.4 0.57/0.68	
Visual acuity, (logMAR)	+1/0	+1/0	+1/0	+1/0	+1/0	+1/0	+1/0
Delivered belamaf (3 weeks before, mg)	NA	170	175	175*	175	175	NA

NA: not applicable; CTCAE: Common Terminology Criteria for Adverse Events; Oxf, Oxford score; n, p or d: none, peripheral or diffuse.
**Exceptionally performed 2 weeks after the previous dose.*

Table 4. Case 4: Follow-up of the symptoms and corneal changes as assessed by slit-lamp and in vivo confocal microscopy according to the therapeutic management.
(Right eye / left eye)

	Week 0	Week 3	Week 5*	6 Weeks after last dose
Symptoms (CTCAE score)				
Blurred vision (0-4)	NA	0 / 0	1 / 1	1 / 1
Photophobia (0-4)	NA	0 / 0	1 / 1	1 / 1
Clinical examination				
Superficial punctuate keratopathy (Oxf)	3 / 1	2 / 1	2 / 2	3 / 2
intraepithelial microcysts (n, p or d)	NA	n / n	p / p	n / n
Central cornea in vivo confocal microscopy				
Epithelial microcysts				
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	0/0 0/0 NA	0/0 0/0 NA
Superficial epithelial hyperreflective deposits				
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	25/0 7.1/0 0.87/NA	18.8/68.8 6.7/9.4 0.84/0.85
Basal epithelial hyperreflective deposits				
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	81.3/0 8.5/0 0.62/NA	18.8/6.3 6.9/5.1 0.74/0.75
Subbasal nerve plexus's layer hyperreflective deposits				
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	6.3/6.3 5.7/5.5 0.78/0.68	18.8/18.8 7.2/9.2 0.59/0.49	12.5/0 6.8/0 0.71/NA
Peripheral cornea in vivo confocal microscopy				
Epithelial microcysts				
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	6.3/18.8 15.2/12.7 0.92/0.91	0/0 0/0 NA
Superficial epithelial hyperreflective deposits				
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	118.8/137.5 8.1/8.5 0.77/0.82	68.8/100 7.4/9.3 0.74/0.80
Basal epithelial hyperreflective deposits				
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	37.5/106.3 7.3/8.7 0.60/0.74	143.8/106.3 8.4/8.0 0.71/0.68	37.5/12.5 5.5/6.2 0.67/0.68
Subbasal nerve plexus's layer hyperreflective deposits				
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	43.8/62.3 7.2/6.4 0.73/0.66	118.8/68.8 9.0/8.3 0.57/0.68	0/18.8 0/6.7 NA/0.65
Visual acuity, (logMAR)	+0.1/0	+0.1/0	+0.2/+0.1	+0.2/0.1
Delivered belamaf (3 weeks before, mg)	NA	155	155	NA

NA: not applicable; CTCAE: Common Terminology Criteria for Adverse Events; Oxf, Oxford score; n, p or d: none, peripheral or diffuse.
**Exceptionally performed 2 weeks after the previous dose.*

Table 5. Case 5: Follow-up of the symptoms and corneal changes as assessed by slit-lamp and in vivo confocal microscopy according to the therapeutic management.
(Right eye / left eye)

	Week 0	Week 3	Week 6	Week 9	Week 12	Week 15
Symptoms (CTCAE score)						
Blurred vision (0-4)	NA	0 / 0	1 / 2	0 / 0	0 / 1	1 / 1
Photophobia (0-4)	NA	0 / 0	2 / 3	1 / 1	1 / 1	1 / 1
Clinical examination						
Superficial punctuate keratitis (Oxf)	0 / 0	0 / 0	1 / 2	0 / 0	0 / 1	1 / 1
Intraepithelial microcysts (n, c, p or d)	NA	p / p	d / d	c / c	d / d	d / d
Central cornea in vivo confocal microscopy						
Intraepithelial microcysts						
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	12.5/6.3 12.6/12.5 0.80/0.77	6.3/12.5 15.5/15.7 0.82/0.68	0/43.8 0/13.9 NA/0.80	0/0 0/0 NA
Superficial epithelial hyperreflective deposits						
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	118.8/193.8 8.8/8.2 0.75/0.68	37.5/62.5 6.1/8.3 0.76/0.73	43.8/125 6.5/9.7 0.74/0.76	0/18.8 0/9.2 NA/0.86
Basal epithelial hyperreflective deposits						
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/18.8 0/6.1 NA/0.73	131.3/231.3 8.6/8.0 0.72/0.70	43.8/37.5 8.1/7.9 0.61/0.62	100/193.8 8.5/8.7 0.68/0.67	75/18.8 6.6/9.6 0.68/0.70
Bowman's layer hyperreflective deposits						
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	31.3/18.8 6.3/6.7 0.63/0.70	87.5/243.8 6.6/8.4 0.64/0.59	25/62.5 7.2/7.0 0.59/0.53	112.5/231.3 9.1/9.5 0.62/0.58	43.8/31.3 6.7/9.8 0.55/0.57
Peripheral cornea in vivo confocal microscopy						
Intraepithelial microcysts						
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	50/62.5 14.9/19.0 0.84/0.79	0/0 0/0 NA	0/6.3 0/12.2 NA/0.99	6.3/0 13.1/0 0.92/NA
Superficial epithelial hyperreflective deposits						

Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	56.3/18.8 8.0/8.2 0.77/0.85	193.8/ 218.8 9.1/8.4 0.86/0. 74	18.8/1 8.8 7.9/7. 2 0.51/0 .79	18.8/68 .8 9.3/8.3 0.76/0. 70	31.3/31. 3 6.3/7.8 0.86/0.7 9
Basal epithelial hyperreflective deposits						
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	162.5/293. 8 10.3/9.2 0.68/0.67	156.3/ 331.3 9.0/8.2 0.71/0. 69	43.8/5 6.3 9.4/7. 5 0.52/0 .70	131.3/1 25 9.1/9.5 0.69/0. 61	56.3/43. 8 8.5/8.8 0.66/0.6 3
Bowman's layer hyperreflective deposits						
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	112.5/243. 8 8.2/7.4 0.60/0.65	150/32 5 9.5/9.0 0.55/0. 60	50/25 7.1/8. 2 0.62/0 .61	100/81. 3 11.4/9. 1 0.59/0. 74	93.8/50 8.3/8.4 0.58/0.4 8
Visual acuity, (logMAR)	+0.2/+0. 1	+0.2/+0.1	+0.2/+ 0.3	+0.1/+ 0.1	+0.1/+0 .2	+0.2/+0. 2
Delivered belamaf (3 weeks before, mg)	NA	162.5	162.5	0	120	120
NA: not applicable; CTCAE: Common Terminology Criteria for Adverse Events; Oxf, Oxford score; n, c, p or d: none, central, peripheral or diffuse.						

Table 6. Case 6 : Follow-up of the symptoms and corneal changes as assessed by slit-lamp and in vivo confocal microscopy according to the therapeutic management.
(Right eye / left eye)

	Week 0	Week 3	Week 6	Week 9	3 weeks after last dose	9 weeks after last dose	3 Months after last dose
Symptoms (CTCAE score)							
Blurred vision (0-4)	NA	0 / 0	1 / 2	2 / 3	1 / 2	0 / 0	0 / 0
Photophobia (0-4)	NA	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Clinical examination							
Superficial punctuate keratopathy (Oxf)	0 / 0	0 / 1	4 / 4	4 / 4	3 / 2	0 / 0	0 / 0
intraepithelial microcysts (n, p or d)	NA	p / p	d / d	d / d	d / d	NA / NA	n / n
Central cornea in vivo confocal microscopy							
Epithelial microcysts							

Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	31.25/25 15.9/76.25 0.86/0.6	31,25/18.75 19.1/35.7 0.81/0.64	25/12.5 19.1/15.8 0.78/0.59	NA/NA NA/NA NA/NA	0/0 0/0 NA
Superficial epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	25/12.5 24/7.5 0.53/0.61	37.5/25 75/26.2 0.49/0.65	20/18.75 29/19 0.53/0.57	NA/NA NA/NA NA/NA	0/0 0/0 NA
Basal epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	18.75/0 15/0 NA	81.25/75 19.5/24 0.68/0.62	81.25/31.25 18.1/22.2 0.76/0.77	81.25/31.25 26/21 0.76/0.73	NA/NA NA/NA NA/NA	25/0 16.8/0 0.75/NA
Subbasal nerve plexus's layer hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	25/43.75 26/13 0.5/0.67	31.25/68.75 53.3/48 0.59/0.6	31.25/37.7 63.5/28 0.57/0.68	31.25/6.25 15.8/23 0.61/0.62	NA/NA NA/NA NA/NA	25/37.5 10.8/22.8 0.76/0.65
Peripheral cornea in vivo confocal microscopy							
Epithelial microcysts							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	37.5/0 17.4/0 0.84/NA	31.25/26.5 25/19.4 0.74/0.69	25/18.75 20.4/19.4 0.79/0.64	NA/NA NA/NA NA/NA	0/0 0/0 NA
Superficial epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	168.7/150 53.3/42.5 0.58/0.59	93.75/56.25 20/16 0.74/0.55	68.75/56.25 29/29.8 0.77/0.54	43.75/31.25 26/23.6 0.51/0.63	NA/NA NA/NA NA/NA	0/0 0/0 NA
Basal epithelial hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	212.5/200 52.1/51.5 0.67/0.7	262.5/168.75 56.2/51 0.65/0.69	268.75/125 38.7/29.8 0.61/0.68	168.75/112.52 26.1/23 0.68/0.68	NA/NA NA/NA NA/NA	0/0 0/0 NA
Subbasal nerve plexus's layer hyperreflective deposits							
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	62.5/2528.4/20.3 0.56/0.61	150/50 30.4/28.1 0.58/0.66	156.25/62.5 21.6/23.3 0.64/	62.5/50 21.3/ 0.62/0.67	NA/NA NA/NA NA/NA	18.75/0 10.8/0 0.53/NA

				0.74			
Visual acuity, (logMAR)	+0.3/+0.4	+0.3/+0.4	+0.5/+0.7	+0.5/+0.3	+0.4/+0.6	+0.3/+0.4	+0.3/+0.3
Delivered belamaf (3 weeks before, mg)	NA	140	140	110	NA	NA	NA
NA: not applicable; CTCAE: Common Terminology Criteria for Adverse Events; Oxf, Oxford score; n, p or d: none, peripheral or diffuse.							

Table 7. Case 7 : Follow-up of the symptoms and corneal changes as assessed by slit-lamp and in vivo confocal microscopy according to the therapeutic management.
(Right eye / left eye)

	Week 0	Week 3	Week 6
Symptoms (CTCAE score)			
Blurred vision (0-4)	NA	0 / 0	0 / 0
Photophobia (0-4)	NA	0 / 0	0 / 0
Clinical examination			
Superficial punctuate keratopathy (Oxf)	0 / 0	0 / 0	0 / 0
intraepithelial microcysts (n, p or d)	NA	n / n	n / n
Central cornea in vivo confocal microscopy			
Epithelial microcysts			
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	0/0 0/0 NA/NA
Superficial epithelial hyperreflective deposits			
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	0/0 0/0 NA/NA
Basal epithelial hyperreflective deposits			
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	0/0 0/0 NA/NA
Subbasal nerve plexus's layer hyperreflective deposits			
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA/NA	0/0 0/0 NA/NA
Peripheral cornea in vivo confocal microscopy			
Epithelial microcysts			
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA	0/0 0/0 NA/NA
Superficial epithelial hyperreflective deposits			

Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA/NA	0/0 0/0 NA/NA
Basal epithelial hyperreflective deposits			
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA/NA	0/0 0/0 NA/NA
Subbasal nerve plexus's layer hyperreflective deposits			
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA/NA	0/0 0/0 NA/NA
Visual acuity, (logMAR)	+0/+0	+0/+0	+0/+0
Delivered belamaf (3 weeks before, mg)	NA	167.5	167.5
NA: not applicable; CTCAE: Common Terminology Criteria for Adverse Events; Oxf, Oxford score; n, p or d: none, peripheral or diffuse.			

Table 8. Case 8 : Follow-up of the symptoms and corneal changes as assessed by slit-lamp and in vivo confocal microscopy according to the therapeutic management.
(Right eye / left eye)

	Week 0	Week 3
Symptoms (CTCAE score)		
Blurred vision (0-4)	NA	2 / 0
Photophobia (0-4)	NA	0 / 0
Clinical examination		
Superficial punctuate keratopathy (Oxf)	0 / 0	0 / 0
intraepithelial microcysts (n, p or d)	NA	n / n
Central cornea in vivo confocal microscopy		
Epithelial microcysts		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Superficial epithelial hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Basal epithelial hyperreflective deposits		

Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Subbasal nerve plexus's layer hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA/NA
Peripheral cornea in vivo confocal microscopy		
Epithelial microcysts		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA
Superficial epithelial hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA/NA
Basal epithelial hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA/NA
Subbasal nerve plexus's layer hyperreflective deposits		
Density (/mm²) *Average size (µm)* *Circularity (0-1)*	NA	0/0 0/0 NA/NA
Visual acuity, (logMAR)	+0/+0	+0/+0
Delivered belamaf (3 weeks before, mg)	NA	200
NA: not applicable; CTCAE: Common Terminology Criteria for Adverse Events; Oxf, Oxford score; n, p or d: none, peripheral or diffuse.		

Figures

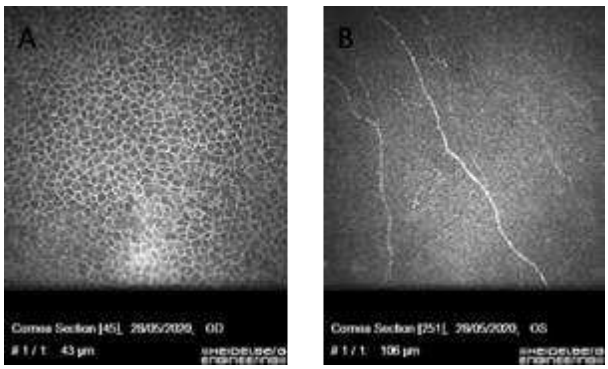

Figure 1. Case 1: First IVCM. (A): corneal epithelium of right eye / (B): Bowman layer (= subbasal nerve plexus layer) of left eye.

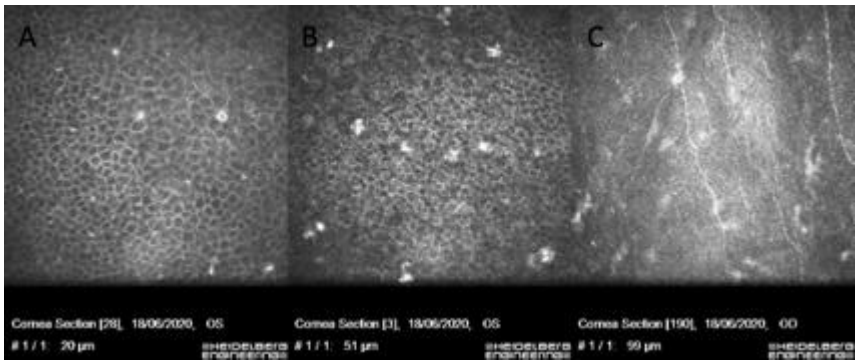

Figure 2. Case 1: IVCM at W3. (A): superficial epithelium of the left eye / (B) basal epithelium of the left eye / (C): Bowman layer of the right eye. Images taken from the peripheral cornea. The examination of central cornea was normal.

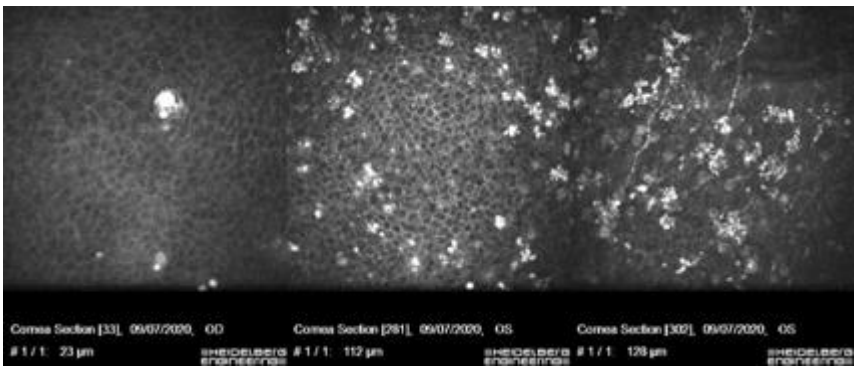

Figure 3. Case 1: IVCM at W6. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the central cornea.

Figure 4. Case 1: Slit lamp examination at W9: Aspect of diffuse microcystic epithelial keratopathy in both eyes.

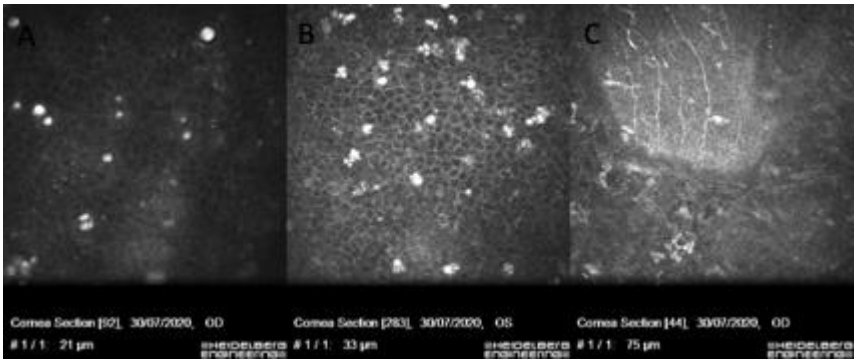

Figure 5. Case 1: IVCM at W9. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman layer of the right eye. Images taken from the central cornea.

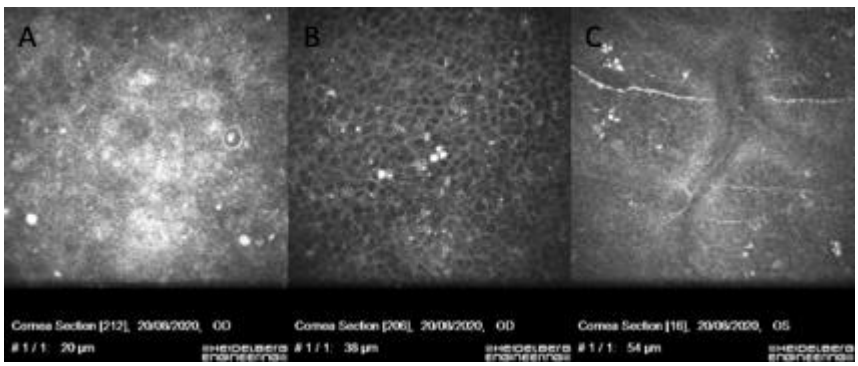

Figure 6. Case 1: IVCM at W12. (A): superficial epithelium of the right eye / (B): basal epithelium of the right eye / (C): Bowman layer of the left eye. Images taken from the central cornea.

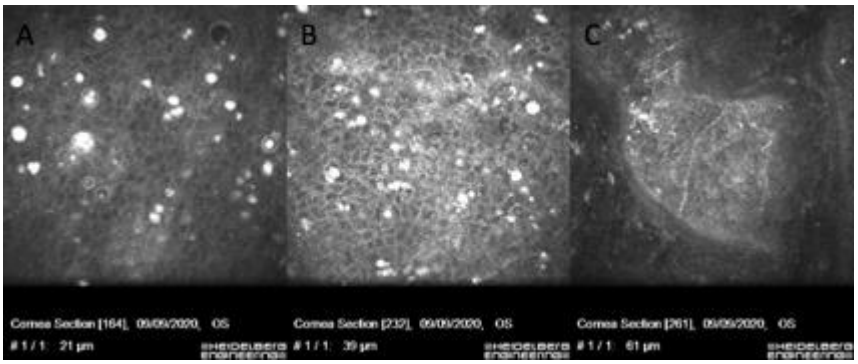

Figure 7. Case 1: IVCM at W15. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the central cornea.

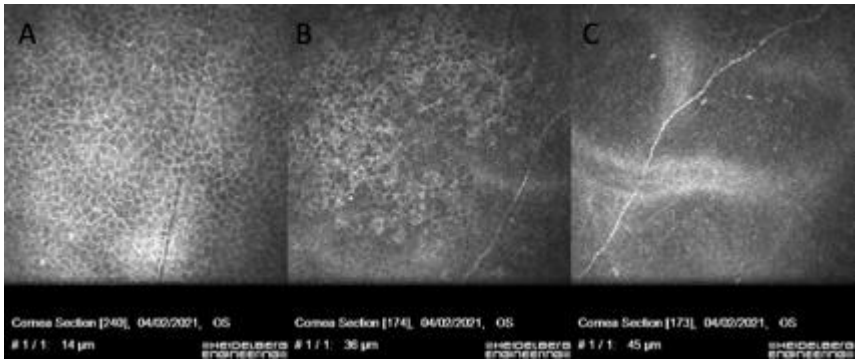

Figure 8. Case 1: IVCM 5 months after stopping treatment. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the central cornea.

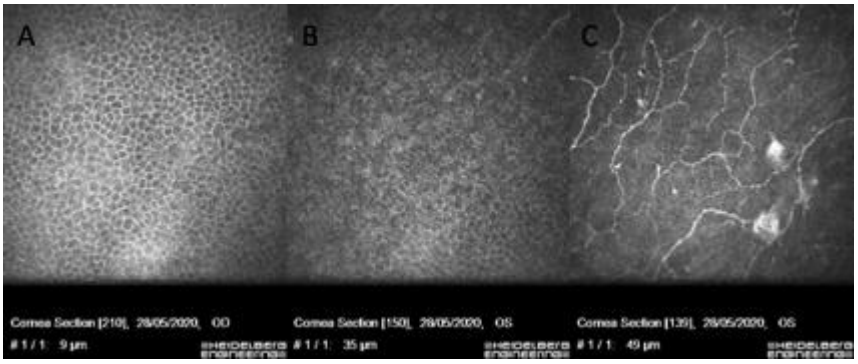

Figure 9. Case 2: First IVCM. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from peripheral cornea.

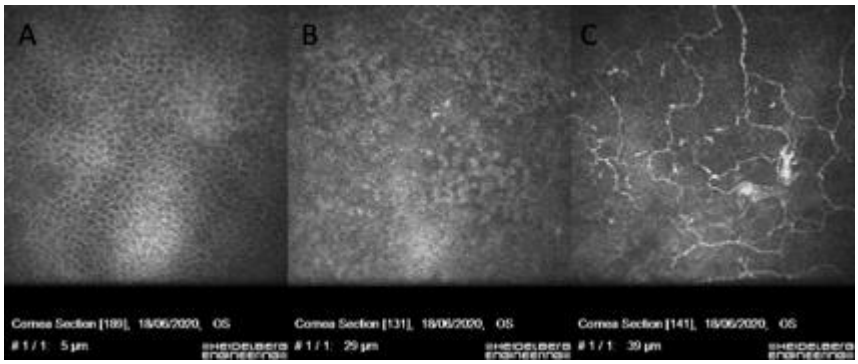

Figure 10. Case 2: IVCM at W3. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the peripheral cornea. Morphological appearance of the right eye was similar. Central cornea was normal.

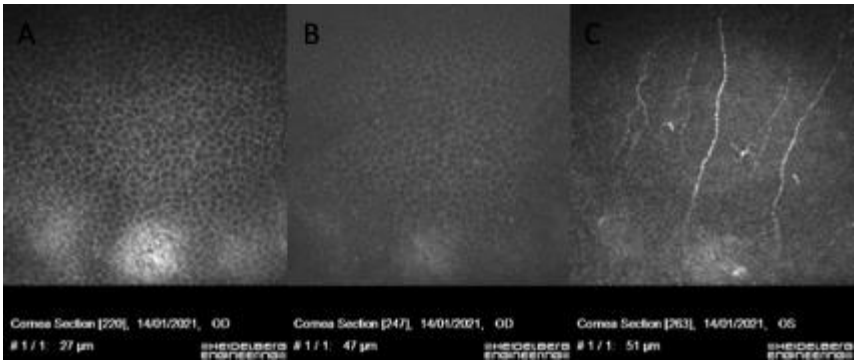

Figure 11. Case 3: IVCM at W3. (A): superficial epithelium of the right eye / (B): basal epithelium of the right eye / (C): Bowman layer of the left eye. Images taken from the peripheral cornea.

Figure 12. Case 3: Slit lamp examination at W6: Aspect of incipient paralimbic keratopathy in both eyes.

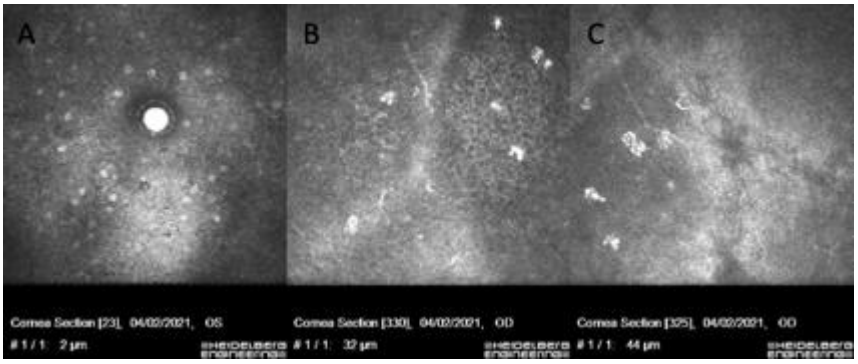

Figure 13. Case 3: IVCM at W6. (A): superficial epithelium of the left eye / (B): basal epithelium of the right eye / (C): Bowman layer of the right eye. Images taken from the peripheral cornea.

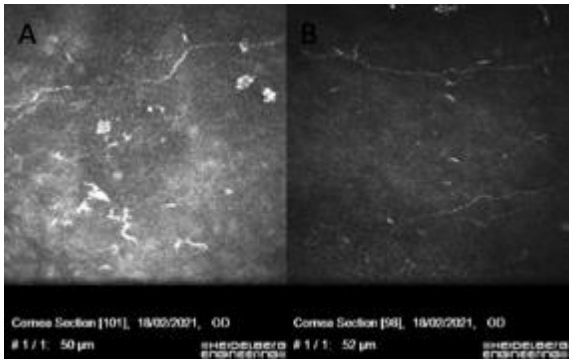

Figure 14. Case 3: IVCM at W8, Right eye. (A) Bowman layer of the peripheral cornea / (B) Bowman layer of the central cornea.

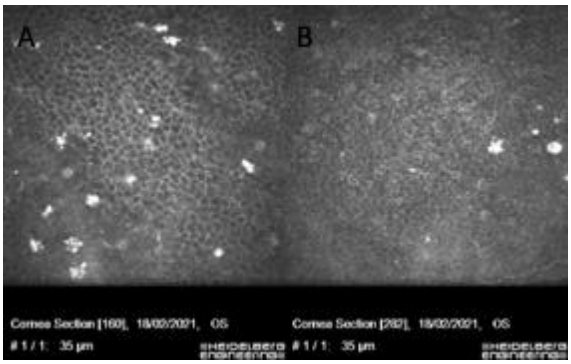

Figure 15. Case 3: IVCM at W8, Left eye. (A) Basal epithelium of the peripheral cornea / (B) Basal epithelium of the central cornea.

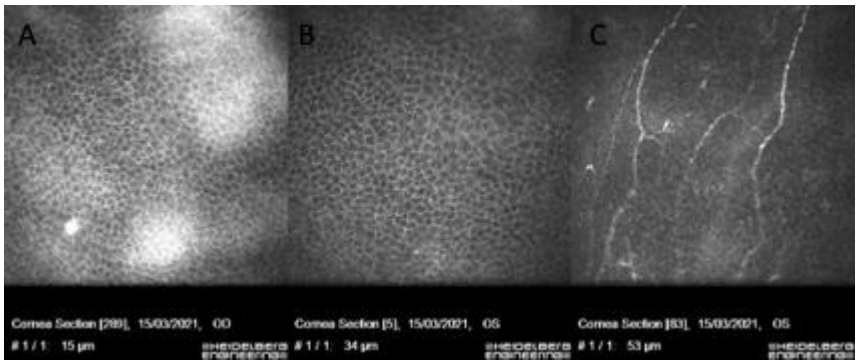

Figure 16. Case 3: IVCM at W12. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images exclusively taken from the central cornea, showing the absence of significant damage at this level after 12 weeks of therapy start.

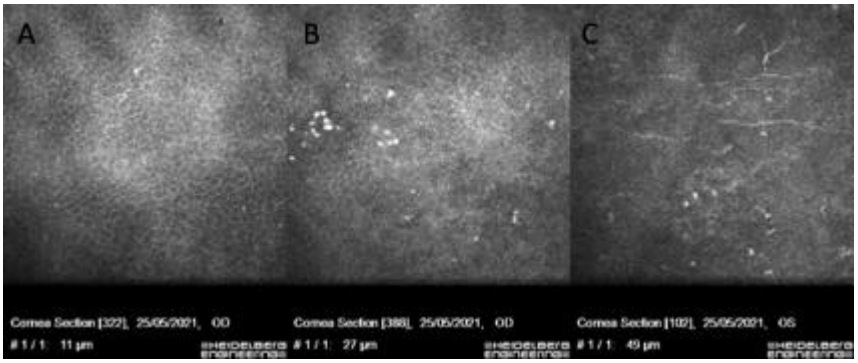

Figure 17. Case 3: IVCM at W22. (A): superficial epithelium of the right eye / (B): basal epithelium of the right eye / (C): Bowman layer of the left eye. Images taken from the peripheral cornea.

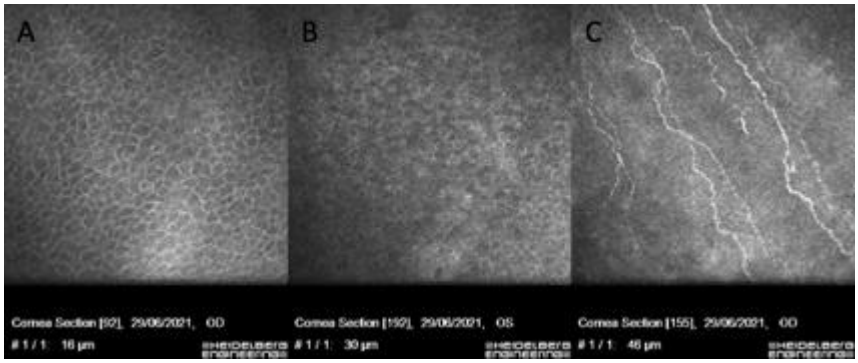

Figure 18. Case 3: IVCM 2 months after last dose. (A): superficial epithelium of the right eye

/ (B): basal epithelium of the left eye / (C): Bowman layer of the right eye. The analysis was normal and similar for the peripheral and central cornea.

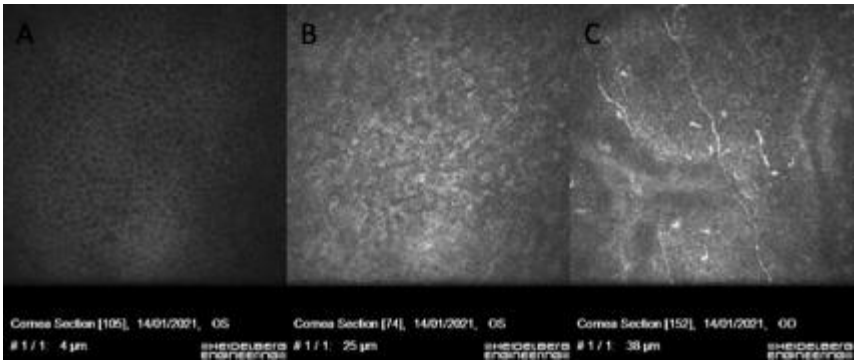

Figure 19. Case 4: First IVCM. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman's layer of the right eye. Images taken from central cornea.

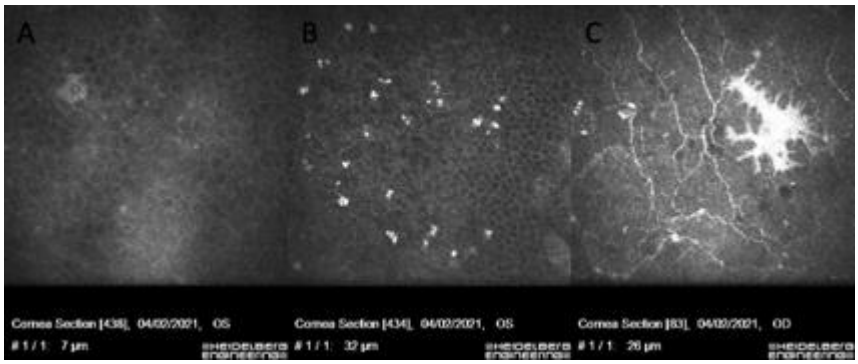

Figure 20. Case 4: IVCM at W3. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the right eye. Images taken from the peripheral cornea. Note that the subepithelial scar lesion of the right eye was not considered in the additional analysis.

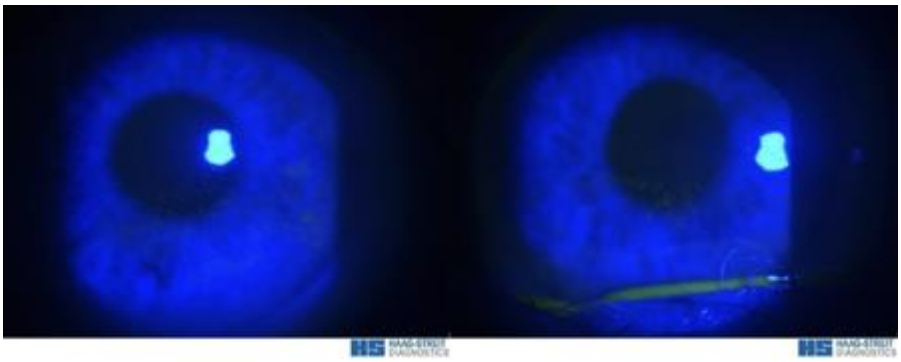

Figure 21. Case 4: Slit lamp examination at W5: Aspect of superficial punctuate keratopathy in both eyes in blue light.

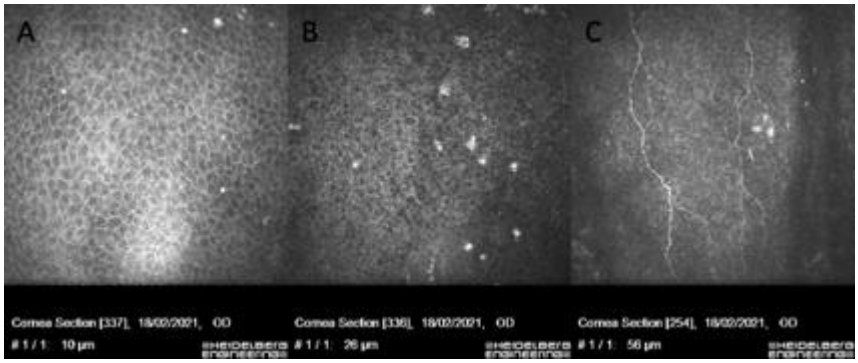

Figure 22. Case 4: IVCM at W5, central cornea. (A): superficial epithelium of the right eye / (B): basal epithelium of the right eye / (C): Bowman's layer of the right eye.

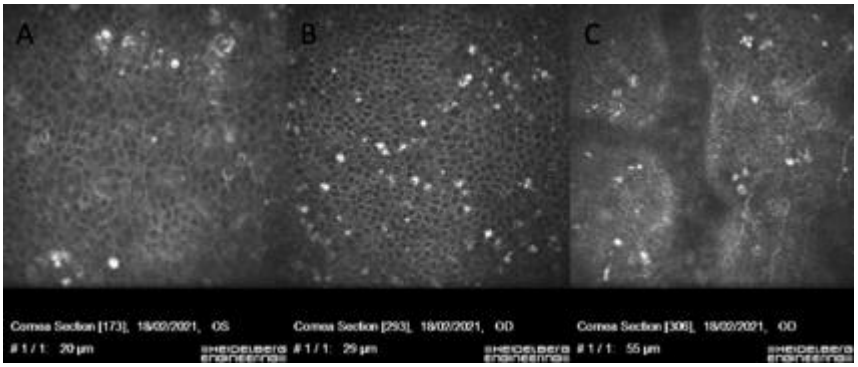

Figure 23. Case 4: IVCM at W5, peripheral cornea. (A): superficial epithelium of the left eye / (B): basal epithelium of the right eye / (C): Bowman layer of the right eye.

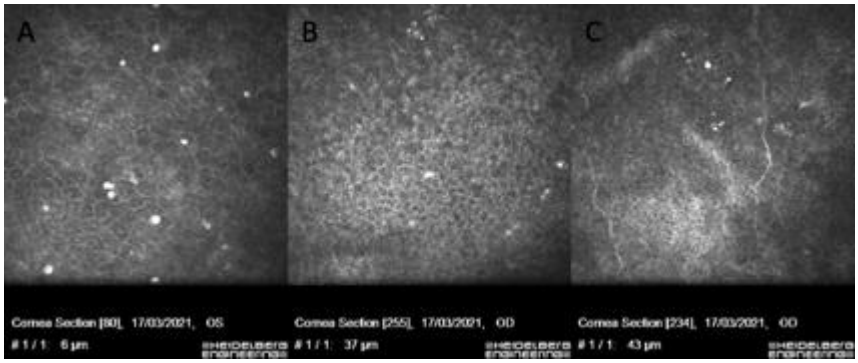

Figure 24. Case4: IVCM 6 weeks after last dose. (A): superficial epithelium of the left eye / (B): basal epithelium of the right eye / (C): Bowman layer of the right eye. Images taken from the central cornea.

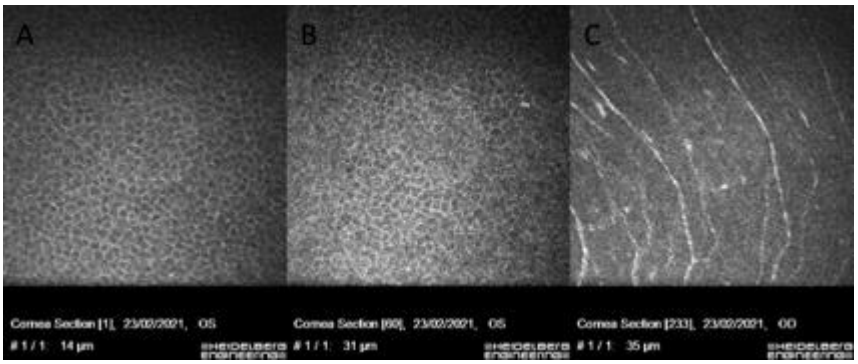

Figure 25. Case 5: First IVCM. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the right eye. Images were similar in both the central and the peripheral cornea.

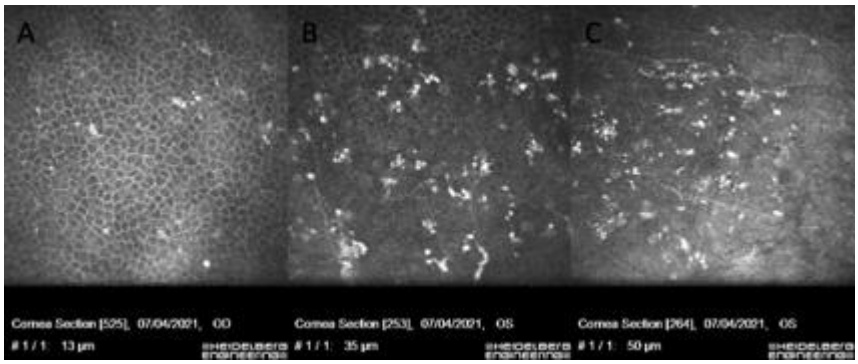

Figure 26. Case 5: IVCM at W3. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the peripheral cornea.

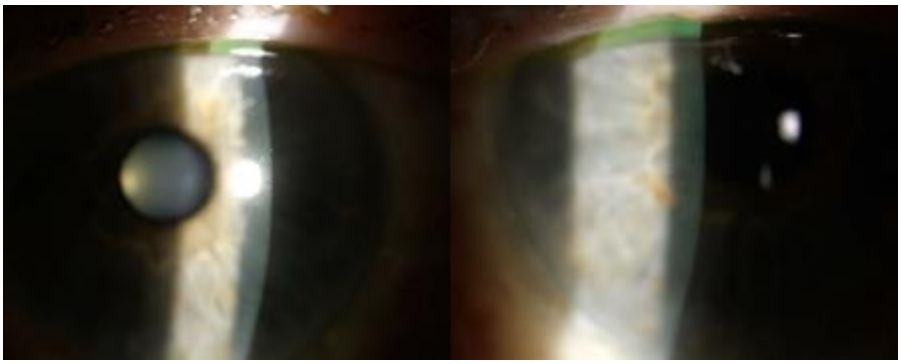

Figure 27. Case 5: Slit lamp examination at W6: Aspect of diffuse microcystic epithelial keratopathy in both eyes.

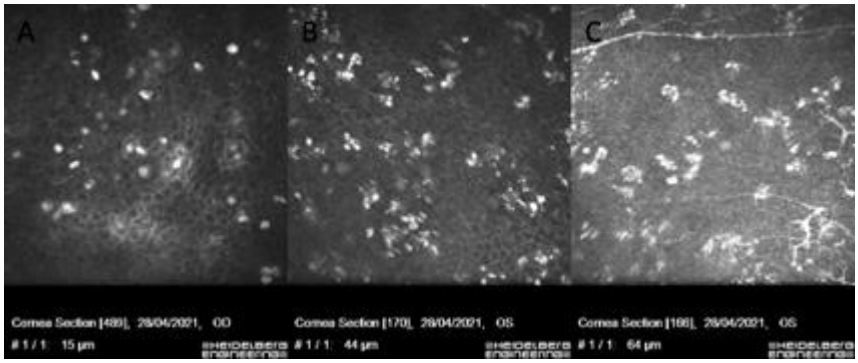

Figure 28. Case 5: IVCM at W6. (A): superficial epithelium of the right eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the central cornea.

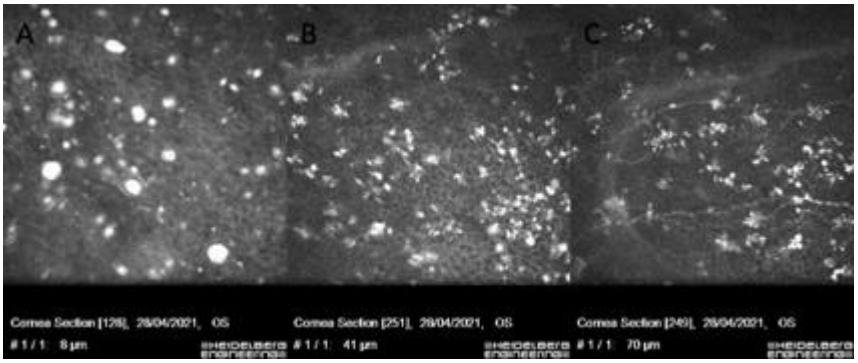

Figure 29. Case 5: IVCM at W6. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the peripheral cornea.

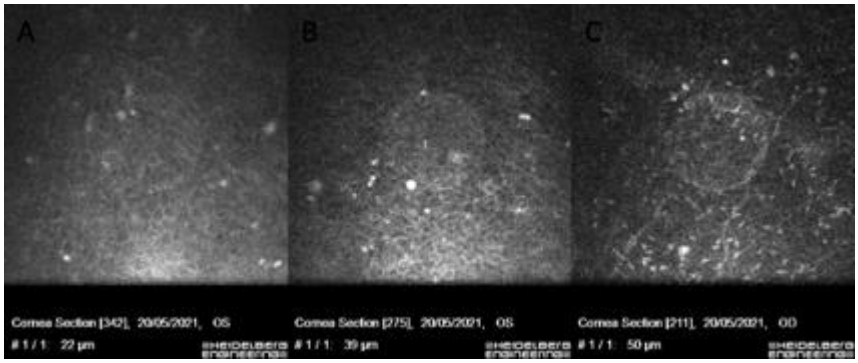

Figure 30. Case 5: IVCM at W9. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the right eye. Images taken from the peripheral cornea.

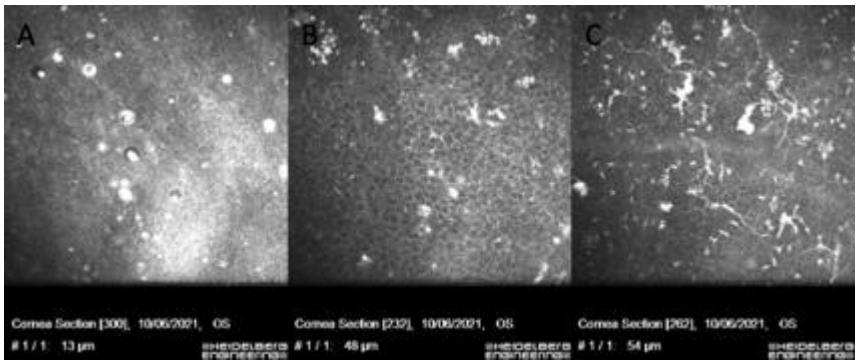

Figure 31. Case 5: IVCM at W12. (A): superficial epithelium of the left eye / (B): basal epithelium of the left eye / (C): Bowman layer of the left eye. Images taken from the central cornea.

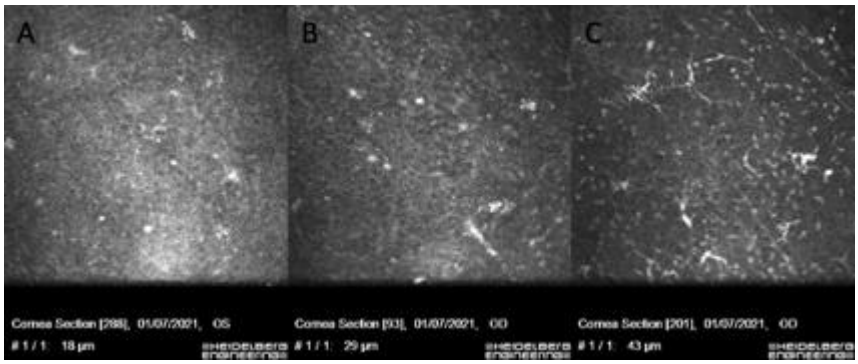

Figure 32. Case 5: IVCM at W15. (A): superficial epithelium of the left eye / (B): basal epithelium of the right eye / (C): Bowman's layer of the right eye. Images taken from the peripheral cornea.

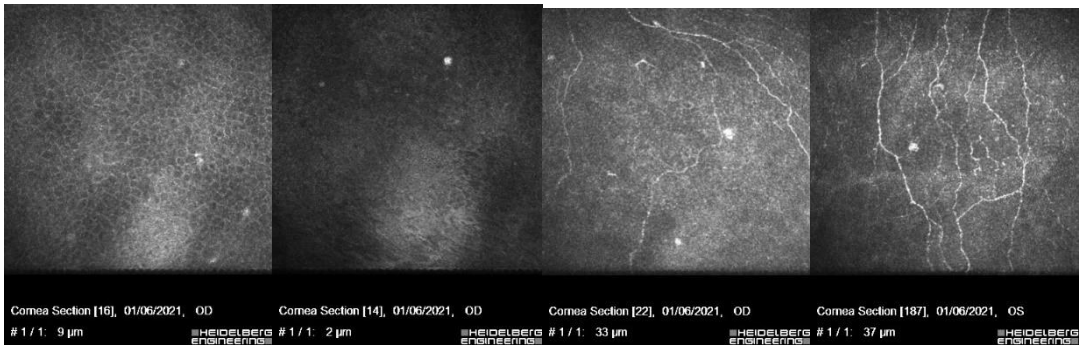

Figure 33. Case 6 : First IVCM of the peripheral cornea. (A) : superficial epithelium of the right eye. (B) Basal epithelium of the right eye. (C) : Bowman's layer of the right eye. (D) Bowman's layer of the left eye.

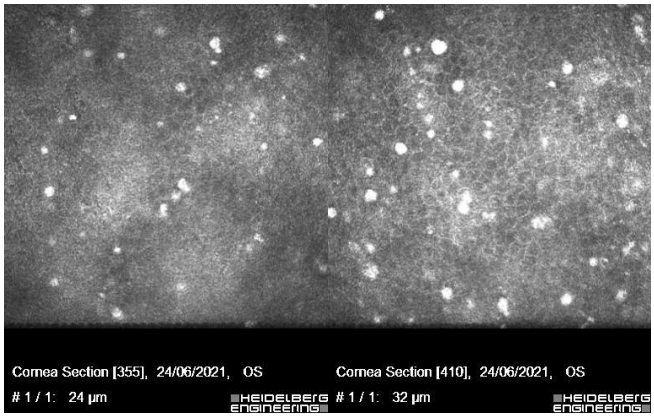

Figure 34. Case 6 : IVCM at W3. (A) Basal epithelium of the periperal cornea of the left eye. (B) : superficial epithelium of the peripheral cornea of the left eye.

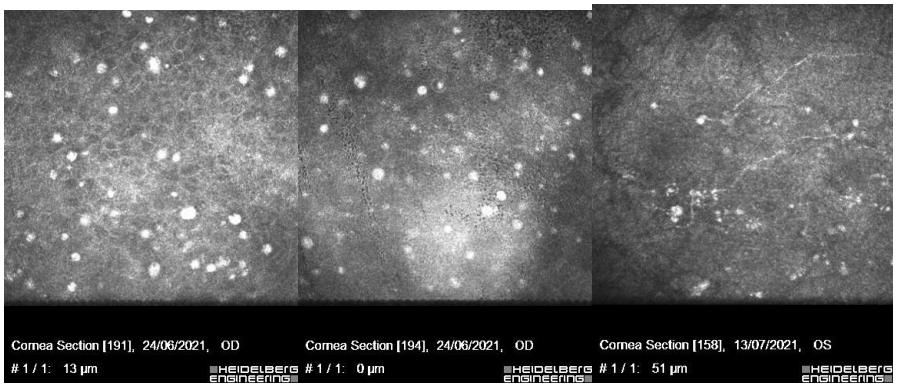

Figure 35. Case 6 : IVCM at W6 : (A) Basal epithelium of the periperal cornea of the left eye. (B) : superficial epithelium of the peripheral cornea of the right eye. (C) Bowman's layer of the peripheral cornea of the right eye.

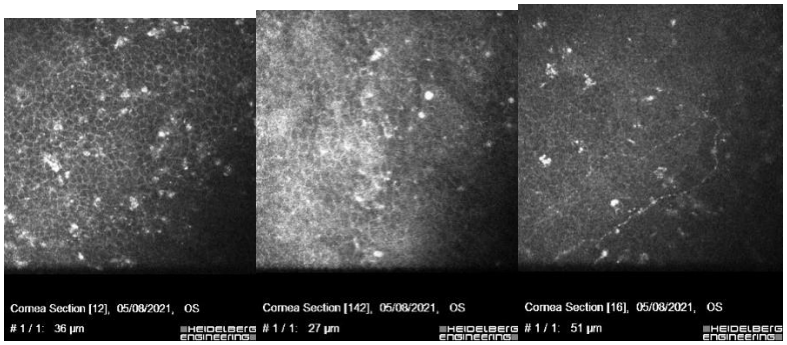

Figure 36. Case 6 : IVCM at W9 : (A) Superficial epithelium of the cornea of the left eye. (B) Basal epithelium of the left eye. (C) Bowman's layer of the left eye.

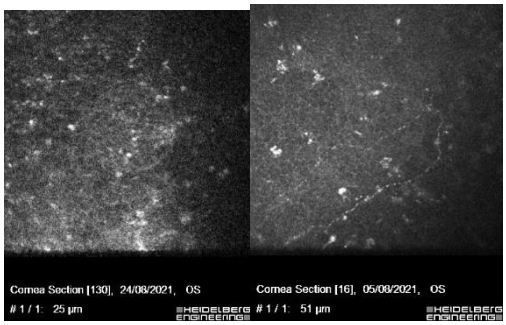

Figure 37. Case 6 : IVCM at W12 : (A) Superficial epithelium of the cornea of the right eye. (B) Bowman's layer of the right eye.

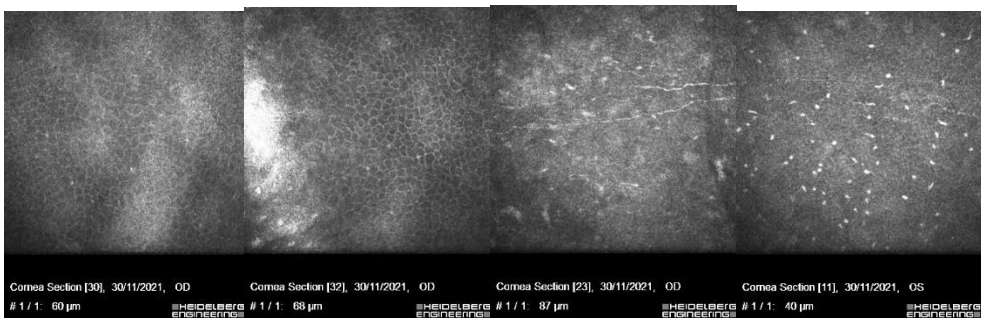

Figure 38. Case 6 : IVCM at W22 : (A) & (B) epithelium of the periphery of the cronea of the right eye. (C) Bowman's layer of the right eye in the periphery of the cornea. (D) Sub basal epithelium of the left eye of the peripheral cornea.

Complete examination at each visit

CASE 1

A 61-years old woman who must start belantamab mafodotin treatment was included. In her history, ~~multiple myeloma~~MM had been diagnosed in 2008 and her disease had already been refractory to 6 previous lines of treatment. The clinical and morphological IVCM follow-up of this patient are summarized in the table 1 (Supplemental Data)

INITIAL REFERENCE EXAMINATION (WEEK 0)

During the first ophthalmologic consultation, which was the reference examination before

initiation of treatment, she reported symptoms of dry eye. She had not any ophthalmic treatment. The slit lamp examination found a superficial punctate keratopathy more significant on left eye (Oxford score at 1 on the right eye and 2 on the left eye), as well as posterior blepharitis with meibomian gland dysfunction evaluated at Stage 2 on the right eye and Stage 3 on the left eye. There was no corneal hypoesthesia. Fundus and macular OCT-SD were normal in both eyes.

A reference imaging in IVCM was carried out, not finding any notable characteristics during this initial evaluation.

At the end of this first consultation, we informed the hematologist of the corneal state and theoretical contraindication to the initiation of this therapy due to the risk of aggravation her corneal pathology, especially for the left eye. After considering our opinion, the hematology department decided to initiate therapy with belantamab mafodotin because of the patient's vital prognosis and the absence of any other therapeutic alternative, which prevailed over than ocular functional risk.

We prescribed an ocular treatment to manage blepharitis and evaporative dry eye including: eyelids massages, artificial tears based on high molecular weight hyaluronic acid and carboxymethylcellulose, monthly cures of azithromycine eye drops, vitamine A eye ointment at bedtime. Therefore, she received a first infusion of belantamab mafodotin at the posology of 180 mg corresponding to 100% of the theoretical dose (2,5mg/kg).

CONSULTATION AT WEEK 3

She reported mild photophobia in the left eye. Visual acuity improved following local treatment initiation.

Slit lamp examination found an early appearance of microcystic keratopathy only on the peripheral cornea without ulceration or visual impact.

IVCM examination found the constitution of discrete clusters of hyperreflective material mainly localized at Bowman layer and basal epithelium. These deposits only affected the peripheral cornea at this moment. The study of the central cornea was superimposed on the initial examination.

Following this consultation, and given the reference consultation data, there was no ophthalmologic contraindication to continuing the hematologic therapy. Therefore, she

received a second infusion of belantamab mafodotin at 100% of the theoretical dose (180 mg).

CONSULTATION AT WEEK 6

Symptoms were dominated by the blurred vision, which was found clinically with a significant visual acuity decrease of 3 lines on the right eye and 5 lines on the left eye. Slit lamp examination found an increase in superficial punctuate keratopathy, as well as microcystic epithelial keratopathy progressing centripetally.

IVCM examination found a worsening of the corneal involvement with an increase in basal epithelium and Bowman's layer hyperreflective deposits, diffusely over the entire corneal surface, forming real « bunch of grapes » shaped clusters. The lesions observed also involved the superficial epithelium of the cornea, until then intact. At this level, the changes had a rounder shape, forming small degenerative intraepithelial microcysts, mostly consisting of a hyper-reflective wall. These were present in large quantities at the level of the corneal periphery but lesser extent in the center of the cornea. All these abnormalities were denser on the left eye, which well correlated with visual acuity decrease on that side.

At the end of this consultation, we informed the hematology department of worsening corneal condition and transmitted a contraindication to the continuation of therapy because of corneal ulcer, infection, and permanent visual loss risks. The hematology department decided to suspend treatment on these recommendations, requesting a revaluation 3 weeks later.

CONSULTATION AT WEEK 9

The patient no longer reported a functional complaint. Visual acuity had returned almost to baseline.

However, on slit lamp we found microcystic keratopathy aspect even more dense, bilateraly (Figure 1).

In IVCM, we observed in both eyes a tendency to migrate towards the superficial of the previously described hyperreflective deposits. Thus, images made at the level of Bowman layer testified the « wash-out » period in the treatment, showing absence of new lesions at this

level. Unlike the entire thickness of epithelium whose analysis still found numerous deposits, interesting more the most superficial layers than before. There was an increase of degenerative microcysts density within the superficial epithelium of the central cornea. Anterior stroma examination was always the same.

At the end of this consultation, taking into consideration the improvement in visual acuity, the reduction in lesions considered to be active in IVCM (reduction of Bowman's layer deposits), we sent to hematology department an opinion of no contraindication to the resumption of treatment but recommending a reduced dosage. The hematology department decided to resume treatment with belantamab mafodotin at a dose reduced to 75% of theoretical dose (130mg in this patient).

CONSULTATION AT WEEK 12

The patient did not report any functional complaints. There was no significant change in visual acuity and slit lamp examination.

In IVCM we found at the level of superficial epithelial layers the appearance of intraepithelial microcysts, still identifiable but less dense. At the level of basal epithelial layers, new deposits were noted in the peripheral cornea only. Surprisingly, despite the new cure 3 weeks ago, Bowman's layer examination was relatively stable with few new active deposits either on the periphery or in the center of the cornea.

Therefore, at the end of this consultation, we had a relative stability of visual acuity, clinical examination in slit lamp as well as appearance in IVCM. We made the same recommendation to hematology department as in the previous consultation. The hematology department administered a further cure of belamaf, still at an equivalent dose to 75% theoretical dose (130mg).

CONSULTATION AT WEEK 15

The patient still didn't report any functional complaints. However, a moderate decrease of visual acuity was noted on the left eye compared to the baseline examination. Clinical slit lamp appearance was stable.

In IVCM, there was at the central cornea an asymmetric increase in basal epithelial deposits,

more important on the left eye. There was also an increase in the density of intraepithelial microcysts into superficial epithelium, again more significantly on the left eye, giving on some images of hyperreflective « balloon release ». For the peripheral cornea, the analysis was similar to the previous consultation.
At the end of this 5th follow-up consultation, the hematology department unfortunately decided to stop treatment with belantamab mafodotin due to a therapeutic failure on RRMM. Therefore, the ophthalmologic follow-up was interrupted but we agreed to a remote examination of her last dose, in agreement with patient, in order to verify the complete reversibility of the corneal damage.

FINAL CONSULTATION 5 MONTHS AFTER LAST DOSE

We had seen the patient ~~distantly~~ 5 months after the last dose of belantamab mafodotin delivered. She did not report functional complaint. Visual acuity had returned to baseline, as was slit lamp examination with disappearance of the microcystic keratopathy.
In IVCM, we had a complete regression of all the lesions with a completely normal morphological evaluation of the cornea (Figure 2).
Therefore, this case testifies to the reversible nature of the corneal iatrogenicity induced by belantamab mafodotin. We stopped the ophthalmologic follow-up of this patient at the end of this last evaluation.

CASE 2

In May 2020, we receive a 77-years-old man who must start treatment with belantamab mafodotin as 4th line of treatment for an RRMM. In his ophthalmologic history, we simply found cataract surgery.
The clinical and morphological IVCM follow-up of this patient are summarized in the table 2 (Supplemental Data).

INITIAL REFERENCE EXAMINATION (WEEK 0)

During the pre-therapeutic consultation, he reported the presence of ocular secretions, especially in the morning. He had no symptoms of dry eye. Visual acuity was measured at 0 LogMAR in both eyes. Intraocular pressure was normal in both eyes.
Slit lamp clinical examination bilaterally found clear corneas, fluorescein instillation found

minimal superficial punctuate keratitis (Oxford score 0), and posterior blepharitis. There was also a slight ectropion in the right eye with simple tilting of the tear point. Corneal aesthesia was normal in both eyes. Fundus and OCT-SD analysis were unremarkable.

A first reference examination in IVCM was carried out not finding any anomaly of the cornea epithelium. However, at the level of Bowman layer we noted the presence of a few hyperreflective anomalies which seemed to be scary looking, only at the level of peripheral cornea. These pre-treatment lesions were not considered in subsequent additional analyzes.

At the end of this consultation, we instituted local treatment with artificial tears and authorized therapy with belantamab mafodotin. Thus, the patient received a first dose at 2.5mg/kg (170mg).

CONSULTATION AT WEEK 3

The patient did not report any functional complaints. Visual acuity was still maintained and stable in both eyes. Slit lamp examination was strictly identical to the previous consultation.

In IVCM, there were minimal hyperreflective deposits in the basal epithelium and Bowman layer, but only within the paralimbic cornea area.

At the end of this consultation, we issued a favorable opinion for the continuation of treatment. The patient received a second infusion of belantamab mafodotin at the dose of 190mg. Unfortunately, the disease quickly turned out to be refractory to this therapy.

Afterwards, the patient could not be reassessed due to a deterioration in his general condition,

particularly with severe anemia and dependence on transfusion. At the beginning of July, it was decided in a multidisciplinary consultation meeting to stop therapy with belantamab mafodotin and start 6th line treatment bortezomib, cyclophosphamide and corticosteroids.

Despite this new attempt of treatment, the patient died 5 months later from his illness.

CASE 3

In December 2020, we receive a 66-year-old man who must start treatment with belantamab mafodotin in 5th line in the management of a RRMM. In his history, we found multiple pathological vertebral fractures related to his hemopathy, which was responsible for a loss of autonomy. Ophthalmologically, he presented severe amblyopia on the right eye since childhood, of inorganic origin.

The clinical and morphological IVCM follow-up of this patient are summarized in the table

3 (Supplemental Data).

INITIAL REFERENCE EXAMINATION (WEEK 0)

During the first pretherapeutic consultation, the patient did not report any functional ophthalmologic sign. Initial visual acuity was measured at +1 LogMAR on the right eye and 0 LogMAR on the left eye. Intraocular pressures were normal.

Slit lamp examination found clear corneas, fluorescein instillation was negative. There was no corneal hypoesthesia in both eyes. The lenses were clear too. Fundus examination as well as macular OCT-SD were normal.

Initial morphological analysis in IVCM was normal in both eyes.

At the end of this first consultation, we gave our agreement to the hematology department for start belantamab mafodotin therapy. As the patient had no complaints and normal clinical examination, we just simply prescribed artificial tears if necessary.

Therefore, the patient received a first dose of belantamab mafodotin at a dosage of 2.5mg/kg (i.e., 170mg).

CONSULTATION AT WEEK 3

The patient was ophthalmologically non-symptomatic. He didn’t need to instill artificial tears.

Visual acuity and slit lamp examination were stable in both eyes, with no noticeable corneal abnormalities.

In IVCM, we mainly noted the appearance of a few very small hyperreflective deposits in Bowman layer, only at the peripheral cornea, bilaterally. Central cornea examination was normal .

Following this assessment, we authorized the continuation of the treatment. Thus, the patient received a second dose of belantamab mafodotin at 100% of the theoretical posology (i.e., 175mg).

CONSULTATION AT WEEK 6

There was still no functional complaint from the patient. Visual acuity was unchanged.

The slit lamp examination found an incipient modification, mainly paralimbic epithelial

keratopathy (Figure 4).

Morphological examination in IVCM showed an increase in hyperreflective deposits mainly in the paralimbic area. At the superficial epithelium, rare images of microcysts could be seen.

Analysis of the central cornea was just a little changed, with the appearance of some deposits within basal epithelial layers but without any refractive or functional repercussions.

We informed the hematology department about this worsening of the morphological impairment, but the continuation of the therapy was authorized due to the absence of functional repercussions. However, we recommended an earlier follow-up consultation 2 weeks later. Therefore, the patient received a new dose of belantamab mafodotin at 175mg.

CONSULTATION AT WEEK 8

The patient still reported no symptoms. Slit lamp examination was stable wis an aspect of non-microcystic paralimbic epitheliopathy. Fluorescein instillation was still negative. There was no corneal hypoesthesia.

Visual acuity was stable in both eyes, although IVCM examination showed increased deposits within the basal epithelium and Bowman layer. This increase in damage mainly concerned the peripheral cornea and to a lesser extent the central cornea, but not enough to affect the patient's visual acuity and quality of life.

Given that the absence of functional repercussions for the patient, we authorized the continuation of treatment. Therefore, the following week the patient received a 4th dose of belantamab mafodotin, at a dose of 175mg. We scheduled a new consultation 3 weeks after this infusion.

CONSULTATION AT WEEK 12

This consultation was marked by deterioration of the patient general condition who presented with a pulmonary infection which led to establishment of continuous oxygen therapy.

However, he still did not report any ophthalmologic complaints. Visual acuity and slit lamp examination were stationary.

The morphological analysis in IVCM was relatively stable, with very few deposits at the

central cornea within the basal epithelial layers, and even less within the more superficial.

Also at the peripheral cornea, there was no worsening of the appearance previously observed.

Paradoxically, although the treatment was continued at the same posology, Bowman's layer and basal epithelium deposits had even decreased in comparison with the last follow-up visit which exceptionally carried out two weeks after the previous dose. Therefore, we can assume for this patient that the lesions are cleaned quickly with a regression of the deposits after two weeks of treatment. There were still no epithelial microcysts.

At the end of this consultation, we had no contraindication to continuing treatment.

Unfortunately, due to his general condition deterioration with oxygen dependence and transfusion dependence for anemia and thrombopenia, the patient was not able to receive the next dose following our consultation. Belantamab mafodotin targeted therapy was suspended and resumed on April 29.

CONSULTATION AT WEEK 22

We convened the patient 3 weeks after the belantamab mafodotin therapy was resumed. However, as the patient was a COVID contact case at the time of this appointment, this follow-up consultation was postponed to the following week. It was therefore performed exceptionally at 4 weeks of the previous dose. Patient still did not report any visual complaints and did not use prescribed artificial tears. His general condition was stabilized, he was no longer on oxygen therapy. Visual acuity was unchanged. Likewise, the slit-lamp examination still found this aspect of paralimbic epithelial keratopathy without microcyst.

In IVCM, the analysis testified to the « wash out » period in patient care. The appearance being very similar to the first 2 follow-up consultations, with few hyperreflective deposits in the peripheral cornea, almost non-existent at the level of the central cornea. Either way, these anomalies still had no refractive impact.

At the term of this consultation, we still had contraindication to continuing treatment with belantamab mafodotin. Even so, patient management was discussed in a multidisciplinary consultation meeting and the therapy with belantamab mafodotin was definitively

discontinued due to a therapeutic failure on RRMM.

FINAL CONSULTATION 2 MONTHS AFTER LAST DOSE

A final consultation was performed 2 months after the last dose of belantamab mafodotin to ensure the reversibility of corneal iatrogenicity induced y this treatment. In terms of his general condition, he had a recent costal fracture related to a secondary lesion of his hematological malignancy. Visual acuity was unchanged.

Slit lamp examination was stable, with even a decrease in the paralimbic epithelium granity aspect. There was still no microcyst and fluorescein instillation was negative.

IVCM analysis found a complete regression of hyperreflective clusters associated with the therapy by belantamab mafodotin (Figure 4).

At the end of this consultation, we stopped the ophthalmological follow-up related to this therapy. The patient then benefited from a 6th line treatment for his RRMM, combining Cyclophosphamide and Prednisone.

CASE 4

In January 2021, we receive a 70-year-old woman for a pre-therapeutic assessment before starting treatment with belantamab mafodotin as part of a stage III IgA kappa RRMM. The diagnosis of his disease was made in 2011, it was the 5th line of treatment. Her malignant hemopathy was responsible for a biological impact with severe cytopenia, she reported iterative transfusions of red blood cell concentrates with already 25 transfusions to her credit at the time of this first consultation. In terms of her other history, she was only treated and well-balanced high blood pressure, as well as cataract surgery of both eyes performed 2 years

earlier.

The clinical and morphological follow-up in IVCM of this patient are summarized in the table 4. (Supplemental Data)

INITIAL REFERENCE EXAMINATION (WEEK 0)

During this first pretherapeutic consultation, the patient reported symptoms such as eye burns,

more important on right eye. These were rather well relieved by artificial tears, prescribed by her usual ophthalmologist. Visual acuity was measured at +0.1 LogMAR on the right eye and

0 LogMAR on the left eye. Intraocular pressures were normal.

On slit lamp examination, there was mainly an aspect of palpebral malocclusion, more important on the right eye. This lagophthalmos was responsible for a superficial punctuate keratitis predominant on the lower part of the corneas and assessed at Oxford 3 on the right eye and Oxford 1 on the left eye. In addition, there was also posterior blepharitis with meibomian gland dysfunction assessed as stage 2 in both eyes. Finally, corneal hypoesthesia favored by chronic palpebral malocclusion was also highlighted. The fundus examination was unremarkable. The OCT-SD analysis did not find any clear anomaly apart from a minimal interruption of the foveolar ellipsoid line on the right eye and a vitreomacular attachment without loss of the foveolar profile on the left eye.

In IVCM, the initial morphological analysis of epithelial layers was unremarkable. On the other hand, at the level of Bowman layer there was a rarefaction of the subepithelial nerves related to chronic lagophthalmos, with also the evidence of a scare-like lesion at the lower part of the cornea on the right eye. This old-looking lesion was excluded from the complementary analysis of density, mean size and circularity measurements of treatment-induced abnormalities.

At the end of this initial assessment, we issued to the hematology department an opinion of theoretical contraindication to the initiation of treatment with belantamab mafodotin because of the high risk of worsening of the patient's corneal condition and visual loss. After consultation with the hematology department, it was nevertheless decided to initiate this therapy because of the potential life benefit which was greater than the theoretical functional risk. Therefore, the patient received a first dose of belantamab mafodotin at 100% of the theoretical dose, i.e.155mg and we scheduled a new consultation 3 weeks after. In order to relieve her symptoms and improve the clinical aspect of her keratopathy, we also prescribed a treatment combining in both eyes: eyelid care, artificial tears, monthly cures of azithromycin and finally vitamin A ointment.

CONSULTATION AT WEEK 3

During this consultation, the patient was relieved by the ophthalmologic treatment introduced.

She did not report loss of vision. However, she had to receive 3 more transfusions or red

blood cell concentrates due to severe anemia. Visual acuity was stable in both eyes.

On slit-lamp examination, there was moderate improvement in the appearance of superficial punctuate keratitis on her right eye, now assessed at Oxford 2. The remainder of the clinical examination was unchanged.

Morphological analysis by IVCM found an onset of iatrogenic involvement exclusively in the basal epithelial layers and Bowman layer of the peripheral cornea. The aspect of the central cornea was unchanged.

Considering the absence of worsening of her ocular condition, we authorized the continuation of the therapy. Thus, the patient received a second dose of belantamab mafodotin at the same posology (155mg). However, to detect as early as possible an extension of the iatrogenic involvement towards the center of the cornea, in this patient whose corneal condition was at risk, we decided to schedule the next follow-up consultation 2 weeks after this second dose.

CONSULTATION AT WEEK 5

The patient again reported some symptoms like eye burns and mild photophobia without impact on her daily activities. She wasn't complaining about visual blur. However, there was a slight decrease in visual acuity, measured at +0.2LogMAR on the right eye and +0.1 LogMAR on the left eye.

The slit lamp examination seemed to find an aspect of incipient microcystic keratopathy at the peripheral area of the cornea. Fluorescein instillation this time was relatively symmetrical with a superficial punctuate keratitis assessed at Oxford 2 in each eye.

In IVCM, the examination showed an aggravation of the ocular toxicity with damages of the superficial epithelial layers at the peripheral cornea including the appearance of some Microcysts (Figure 5), but especially an extension of the iatrogenicity towards the central cornea, which was until then intact. At this level we found hyperreflective clusters at the basal epithelial layers and the Bowman layer, more importantly. These changes were more importantly on the right eye. Anterior stroma examination was always the same (Figure 6).

At the end of this new ophthalmological assessment, due to the increased morphological impairment in IVCM but without significant impact on patient's visual acuity, we authorized

the continuation of treatment but with a recommendation to reduce the posology at 75% of the theoretical dose. Unfortunately, following a multidisciplinary consultation meeting, the hematology department informed us of their decision to stop the therapy by belantamab mafodotin due to a therapeutic failure on her RRMM. Then, she benefited from the initiation of 6th line treatment combining Bortezomib, Cyclophosphamide and Dexamethasone. We still scheduled a final check-up 1 month later (6 weeks after the last dose) to ensure the regression of the iatrogenic corneal damage.

FINAL CONSULTATION 6 WEEKS AFTER LAST DOSE

Symptoms were still dominated by sensations of eye burns and photophobia, but this time the patient also reported a blurred vision in both eyes, although she had not previously complained. She told us about her deterioration in her general condition and her difficulty to instill her eye drops. Visual acuity was reduced to +0.3LogMAR on the right eye and +0.2 LogMAR on the left eye. This measurement was unreliable that day due to the patient's symptoms making it difficult to assess visual acuity correctly.

The slit-lamp examination was marked by the increase in superficial punctuate keratitis assessed at Oxford 4 in both eyes. There were no longer any detectable signs associated with belantamab mafodotin toxicity. The rest of the exam was unchanged.

In IVCM, the morphological analysis found a clear regression of the anomalies considered to be active, mainly the basal epithelial layers and Bowman's layer deposits. At the level of the superficial epithelial layers, there were still some hyperreflective deposits, rather round in shape, which correspond to the final pathway of these toxic degenerative lesions whose kinetics follow the corneal epithelial renewal.

Therefore, this last ophthalmologic assessment found a functional degradation of the patient mainly linked to the worsening of neurotrophic keratopathy due to her chronic lagophthalmos, and not linked to the belantamab mafodotin toxicity which, for its part, had decreased. We have adapted her local treatment in particular with insisting on the systematic application of vitamin A nocturn occlusive. Unfortunately, this patient died 12 days later from her hematology malignancy.

CASE 5

In February 2021, we receive a 69-year-old woman for a pretherapeutic evaluation before starting therapy by belantamab mafodotin in the context of MM refractory to 4 previous lines of treatment. Her malignant hemopathy was responsible for pathological bone fractures at the origin of persistent chronic pain. Biologically, there was no major impact of her illness. In her other history, hepatorenal polycystosis and multinodular goiter were noted

The clinical and morphological ophthalmological follow-up as well as the therapeutic adaptation decision at the end of each check-up are summarized in the Table 5.

INITIAL REFERENCE EXAMINATION (WEEK 0)

During this first consultation, she did not report any visual complaints. Visual acuity was measured at +0.2 LogMAR on the right eye and +0.1 LogMAR on the left eye. Intraocular pressure was normal in both eyes.

Slit lamp examination found clear corneas, fluorescein instillation showed normal epithelium. Nevertheless, there was bilateral corticonuclear cataract responsible for her moderate visual acuity loss. Eyelids and conjunctiva appeared normal. There was no corneal hypoesthesia. Fundus and OCT-SD assessment were without significant anomalies.

The initial morphological evaluation in IVCM confirmed the normal character of the corneal epithelium as well as well as the Bowman layer.

Following this first evaluation, we agreed to start therapy with belantamab mafodotin, considering the absence of contraindication in this patient. We also prescribed artificial tears when needed. Thus, she received a first dose at 100% of the theoretical dose, i.e. 162.5mg. This was carried out on March 19, we planned a follow-up consultation 3 weeks later.

CONSULTATION AT WEEK 3

The patient was ophthalmologically asymptomatic. Visual acuity was stable. Slit lamp examination found an aspect of incipient paralimbic microcystic keratopathy. Fluorescein instillation was negative.

In IVCM, there was mainly toxic damage to the peripheral cornea with the presence of irregularly shaped hyperreflective clusters within the basal epithelium and Bowman layer. Also, the superficial epithelium already had hyperreflective deposits, but less dense and more round in shape. The central cornea did not show any significant sign of iatrogenicity at this

moment, except for a few very small deposits in Bowman layer.

Due to the absence of functional impact, we agreed to continue therapy but warned the hematology department of this early onset of iatrogenicity. Thus, she received a second dose of belantamab mafodotin at the same posology (162.5mg).

CONSULTATION AT WEEK 6

This time, the ophthalmologic functional signs were present and dominated by eye burns sensations, photophobia, and a blurred vision. These symptoms were more severe on the left eye. Visual acuity was stable at +0.2 LogMAR on the right eye, but significantly decreased at +0.3 LogMAR on the left eye.

Slit lamp examination was marked by an increase in the appearance of microcystic keratopathy, now which was diffuse throughout the corneal area. There was also a superficial punctuate keratitis evaluated at Oxford 1 in both eyes. Corneal sensitivity was still normal.

Corneal morphological analysis in IVCM found an increase in the density of the lesions previously described in the peripheral cornea, there was also the presence of microcyst within the superficial epithelium. Examination of the central cornea, which until then had been almost intact, now showed numerous hyperreflective deposits involving all epithelial layers. This toxicity was measured more densely on the left eye than the right eye, which was consistent with the visual acuity loss found. Anterior stroma examination was always the same (Figure 7).

At the end of this consultation, due to the patient's symptoms and especially her grade 3 visual acuity loss on the left eye, we recommended the suspension of treatment. Therefore, she did not receive a new dose and we reassessed the situation 3 weeks later. We encourage the patient to instill artificial tears regularly to relieve her symptoms.

CONSULTATION AT WEEK 9

The patient attested an improvement in her symptoms with less photophobia and less blurred vision. Concerning her general condition, she had to receive 5 new radiotherapy sessions for

the treatment bone lesions secondary due to her hematologic malignancy. Visual acuity had recovered well to +0.1 LogMAR bilaterally.

Slit lamp examination found a migration of microcystic keratopathy appearance affecting only the central and paracentral area of the cornea. Fluoresceine instillation returned negative as at baseline.

In IVCM, there was an overall decrease in deposits on all epithelial layers and Bowman layer, both in the center and the periphery of the cornea. Although superficial microcysts persisted in the center of the cornea, this did not affect the patient's visual acuity (Figure 9).

Given the improvement in visual acuity and morphological appearance in IVCM, we authorized the resumption of therapy with belantamab mafodotin. However, in order to limit the visual impact and the occurrence of a further significant reduction in visual acuity, we recommended to reduce the posology at 75% of the theoretical dose. Thus, in agreement with the hematology department, the patient received a new dose at 120mg.

CONSULTATION AT WEEK 12

During this consultation, she again reported blurred vision on the left eye but without significant impact on her daily activities. She still presented a slight photophobia. These symptoms were well relieved by artificial tears. Visual acuity was stable on the right eye. Concerning the left eye, it was moderately reduced compared to the previous consultation, measured at +0.2 LogMAR. On slit lamp, we still found the appearance of microcystic keratopathy, again in a diffuse way. Fluorescein instillation revealed a superficial punctuate keratitis assessed at Oxford 0 on the right eye and Oxford 1 on the left eye.

IVCM analysis showed an increase in hyperreflective deposits at the central cornea, in particular within basal epithelium and Bowman layer, more importantly on the left eye, which was still a times consistent with the patient 's visual acuity. At the peripheral cornea, an increase in the density of lesions was also noted, but in a less important way than following doses at 100% of theoretical dosage, which could suggest a lesser future toxicity with this new posology.

At the end of this new evaluation, we gave our agreement for the continuation of the therapy but still at the dosage corresponding to 75% of the theoretical dose, although the wish of hematology department was to increase the dose of treatment. Thus, the patient received a

further dose of belantamab mafodotin at 120mg.

CONSULTATION AT WEEK 15

The patient had indeed received a new dose of belantamab mafodotin following our previous evaluation, however the patient's situation was discussed again during a multidisciplinary consultation meeting ten days later which it was decided this therapy because of a therapeutic failure from her MM. The conclusion of this meeting was to be able to offer, unfortunately, only palliative care for this patient. We still maintained our consultation scheduled to follow the regression of corneal iatrogenicity.

The functional signs were dominated by a slight blurred vision in both eyes and still photophobia well relieved by artificial tears. Visual acuity was this time measured at +0.2 LogMAR bilaterally. Slit lamp examination was generally stable except of a slight increase in superficial punctuate keratitis on the right eye assessed at Oxford 1.

In IVCM, surprisingly we observed a decrease in the toxic deposits' density, both in the center and the periphery of the cornea. This probably indicates a dose-dependent effect in this patient with a lower iatrogenicity induced at 75% of the theoretical dose.

Due to the decision of the hematology department, we have interrupted the ophthalmological follow-up linked to this target therapy. Nevertheless, we agreed with the patient for a more remote control to verify the complete regression of her toxic corneal abnormalities, if her general condition allowed it, which the patient accept.

CASE 6

In June 2021, we received a 74-year-old man for a pre-therapeutic evaluation before starting therapy by belantamab mafodotin in the context of MM refractory to 5 previous lines of treatment. He presented a pancytopenia which was transfused several times, and a severe kidney failure requiring dialysis. On the ophtalmological plan, our patient did not complain about anything ans has nerver experimenced any ocular issues.

The clinical and morphological ophthalmological follow-up as well as the therapeutic adaptation decision at the end of each check-up are summarized in the Table 6 (Supplemental Data)

INITIAL REFERENCE EXAMINATION (WEEK 0)

Visual acuity was measured at +0.3 LogMAR on the right eye and +0.4 LogMAR on the left eye. Intraocular pressure was normal in both eyes.

Slit lamp examination found clear corneas witha gerotoxon, an epithelial dystrophy of granular appearance predominantly in the periphery. Fluorescein instillation didn't show any abnormalities. His conjunctiva was healthy. There was a Meibomus gland dysfonction and a clinical impact corticonuclear cataract in both eyes.

Fundus found an excavation estimated at 0.5 symmetrically, and OCT-SD assessment was without significant anomalies.

The initial morphological evaluation in IVCM showed a pre existing sub-epithelial dystrophy, with hyperreflective deposits, more present in periphery.

That IVCM observation raised a problem for us : how will we be able to distinguish the deposits caused by belamaf from those caused by his corneal dystrophy ?

Still, we decided to include him in our study and did all the density measures and calculations in the central area of the cornea and to ensure a clinical surveillance every three weeks.

Following this first evaluation, we agreed to start therapy with belantamab mafodotin, considering the absence of contraindication in this patient. We also prescribed artificial tears when needed. Thus, he received a first dose at 100% of the theoretical dose, i.e. 140 mg.

CONSULTATION AT WEEK 3

The patient was ophthalmologically asymptomatic. Visual acuity was stable. Slit lamp examination also found a stable aspect. Fluoresceine instillation was negative.

In IVCM, there was a beginning of toxicity mainly in the peripheral cornea, with the presence of hyperreflectivity clusters within the basal epithelium and Bowman layer.

Also, the superficial epithelium already had hyperreflective deposits, but less dense and more round in shape. The central cornea did not show any significant sign of iatrogenicity at this moment, except for the already known deposits in relation to his granular dystrophy.

Due to the risk of functional impact, we agreed to continue therapy but warned the hematology department of this early onset of iatrogenicity. Thus, we advised to reduce the posology at 75% for the second dose of belantamab mafodotin.

Given the vital stakes of this treatment, the patient nevertheless benefited from a full dose of 2,5 mg/kg (140 mg).

CONSULTATION AT WEEK 6

This time, the patient complains about a moderate loss of vision but di didn't feel pain or eye burns. Visual acuity was measured at 0,5 in the right eye and +0,7 for the left one.

Slit lamp examination showed an important Superficial Punctuate Keratitis (oxford 4) and a diffuse epithelial microcystic keratopathy.

Corneal morphological analysis in IVCM found an increase in the density of the lesions previously described in the peripheral cornea, there was also the presence of microcyst within the superficial epithelium. Examination of the central cornea, , now showed numerous hyperreflective deposits involving all epithelial layers.

In order to quickly improve our patient's vision, we gave him artificial tears at the posology of 8 drops a day for each eye and notified to our hematologsts colleagues to lower the next dose of treatment. The patient received 1,92 mg/kg of belantamab mafodontin.

We organised a new appointment with our patient 3 weeks later.

AT WEEK 7

The patient asked for the Ophtalmological Emergency Room for a brutal apparition of redness in the right eye.

Slit lamp examination found a sectorial (temporal) subconjunctival hemmorrhage of the right eye. The surface corneal condition was pretty much identical than the previous week.

We looked for a possible traumatism, a hypertensive condition without any success. In that context, we requested a blood test, trying to highlight an hémostasis issue.

We found a thrombocytopenia at 28G. The patient were readressed to the hematology department and benefited from platellets transfusion.

CONSULTATION AT WEEK 9

The patient attested an improvement in his symptoms in the left eye : less blurred vision, but was still annoyed about the right one. The visual acuity was +0,5 in the rigth eye and +0,3 in the left one.

Slit lamp examination still showed a Superficial Punctuate Keratatis stage 4 on the Oxford scale and a diffuse microcystic keratopathy.

In IVCM, there was an overall stability of the deposits in all epithelial layers and Bowman layer, in the center of the cornea and a slight increasing of those in the periphery of the cornea. Superficial microcysts persisted in the center of the cornea, but it's hard to identify precisely which one of the dryness or the iatrogeny is responsibleof the blurry vision of the right eye.

About the MM evolution, a change in the cure was decided, relying on the limited efficacity of the Belamaf and the side effects, ocular in priority. It was decided that he patient will now receive Bendamustine.

A control consultation was requested 3 weeks later.

CONSULTATION AT WEEK 12

The patient had stopped the Belamaf since 6 weeks when we got to see him again to check on his ophtalmological condition.

The visual acuity struggles to recover, especially for the left eye this time. On the right eye we found +0,4 whereas +0,6 for the left one.

About the slit lamp examination, we could observe an important regression of the subepithelial microcysts on both eyes. Fluorescein instillation still showed SPK Oxford 3 in the right eye and Oxford 2 in the left eye.

In IVCM, we saw a persistance of the diffuse subepithelial microcysts and hyperreflective deposits in each layer of the central cornea and of the periphery of cornea, although the patient didn't get the treatment for 6 weeks.

We suggested to re examine him in 6 weeks to evaluate the start of recovery.

CONSULTATION AT WEEK 18

When we saw the patient, he felt a great improvement of his symptomatology.

His visual acuity confirmed his feeling as we measured +0,3 on the right eye and +0,4, which is identical as the pretherapeutic exam.

He didn't report any particular events otherwise.

The slit lamp examination showed a spectacular improvement of his surface, with the complete disparition of the SPK thanks to a great therapeutic compliance from our patient that cured the dry syndrome, and a clear decrease of the microcysts.

Unfortunately, that day, the IVCM was not usable because of some network connection problem.

We suggested to the patient a one month follow up to confirm the transient nature of the toxicity and the complete regression of the lesions.

CONSULTATION OF WEEK 22

Our patient reports no complain about his eyes. He has recovered his pre therapeutic vision.

Slit lamp exam couldn't put in evidence any cysts, nore SPK.

IVCM confirmed that all the specific deposits in relation with the belantamab mafodotin had disappeared. We could note that small round hyperreflective deposits in favor of inflammation can be individualized in the different layers.

We decided to stop the systematic follow-up and we suggested to see the patient again in case of ophtalmological functional signs, such as disabling corticonuclear cataract especially.

CASE 7

In June 2021, we received a 65-year-old man for a pre-therapeutic evaluation before starting therapy of belantamab mafodontin because the five previous cures did not prevent the worsening of his MM.

The patient was regularly transfused for an anemia.

The clinical and morphological follow-up in IVCM of this patient are summarized in the

table 7 (Supplemental Data)

INITIAL REFERENCE EXAMINATION (WEEK 0)

That day, he did not present any ophtalmological history nor current symptoms. Visual acuity was +0 in both eyes. Slit lamp examination of anterior segment of both eyes, intra ocular pressure, fundus, and and IVCM were all within norms.

Therfore, there was no contraindication to start Belamaf at the posology og 2,5 mg/kg.

We gave an appointment 3 weeks later, before the possible second cure of treatment.

CONSULTATION AT WEEK 3

Symptomatology was still none. Examination wasn't modified. Cornea was clear, no evidence of apparition of microcysts, fluoresceine instillation was negative with a normal BUT.

Besides, all additional exams were stable, specially MCIV which was superimposable.

We authorized the delivery of a new full posology cure of treatment (2,5 mg/kg) and we controlled 3 weeks later.

CONSULTATION WEEK 6

Ther was still no ocular complains.

Visual acuity remained +0. Cornea was clear, no evidence of apparition of microcysts, fluoresceine instillation was negative with a normal BUT.

MCIV did not show any sign of iatrogenicity of the treatment.

We gave approvement to continue the treatment at the same posology but because of biological worsening, it was decided to switch for Endoxan.

We organised a control consultation but patient's general condition has deteriorated and the patient was weakened.

CASE 8

In June 2021, we received in pre-therapeutic consultation a 74-year-old man.

He was a candidate to move to a 6th line treatment for his RRMM. The patient was pancytopenic with a severe renal insufficiency.

The clinical and morphological follow-up in IVCM of this patient are summarized in the

table 8 (Supplemental Data)

INITIAL REFERENCE EXAMINATION (WEEK 0)

On the ophtalmological plan, patient was already followed by his usual ophtalmologist for a bilateral cataract with no surgical necessity for the moment. Moreover, the patient is bothered by an old epiphora and tingling of both eyes, in connexion with blepharitis, treated with eyelid massages, warm compresses, and artificial tears.

Visual acuity was measured +0 in the right eye, and +0,1 in the left one. IOP was normal.

Slit lamp examination of the right eye showed a clear central cornea, a senile arch in the periphery, an inferior sub-epithelial scar related to an old intracorneal foreign body, a superficial punctuate keratitis oxford 1 but no other fluoresceinic impregnation. The Break Up Time wasn't superior to 6 seconds and we confirmed the observation of a cataract and a persistant posterior blepharitis. Fundus was normal.

On the left eye, slit lamp examination found a clear central cornea, a senile arch in the periphery. Fluoresceine was negative. The Break Up Time wasn't superior to 6 seconds and we also confirmed the observation of a cataract and a persistant posteriori blepharitis. Fundus was normal.

We practiced a first IVCM that did not find obvious anomalies.

That's why at the end of our first consultation, we agreed to a 2,5 mg/kg introduction of belantamab mafodontin.

CONSULTATION AT WEEK 3

On a general level, the patient developped fever after the last dose of chemotherapy, associated with a high blood pressure and a deterioration of his general condition.

Visual acuity was measured +0 in both eyes.

Slit lamp examination was identical, as well as IVCM, that did not show any corneal iatrogenic toxicity.

We gave our agreement to a new 2,5 mg/kg dose of treatment.

Unfortunately, related to the deep worsening of general condition and according to the patients's wishes, palliative care is decided.