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ORIGINAL ARTICLE

Eye amputation following lifitegrast treatment for ocular graft-versus-host disease: First case report

Premier cas clinique : éviscération suite à un traitement par lifitegrast pour maladie du greffon contre l'hôte oculaire

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Summary Graft-versus-host disease (GVHD) is a common complication in patients undergoing allogeneic stem cell transplantation for acute myeloblastic leukemia that could be very difficult to treat. Lifitegrast 5% (Xiidra@, Novartis), a new immunosuppressive eye drop, was recently approved by the FDA for the treatment of severe dry eye and is currently under review by the European Medicines Agency. In France, lifitegrast has been approved by the French authorities for temporary use in refractory dry eye syndrome resistant to tear substitutes and topical cyclosporine. To date, serious complications have been reported only exceptionally. In this article, we report the case of a 65-year-old patient with a medical history of acute myeloid leukemia (AML) diagnosed in 2015 who received a first matched related donor transplant. In 2019, this patient developed chronic GVH involving the skin, oral mucosa and eye. Despite taking topical and systemic medications for 3 months, the patient did not report relief of

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ocular symptoms. Therefore, lifitegrast was prescribed. To our knowledge, we report the first case of corneal perforation in which evisceration was required following treatment with topical lifitegrast for chronic GVH. In the case presented here, it can be assumed that the underlying mechanisms leading to corneal perforation are multifactorial. Using drug accountability criteria, lifitegrast appears to be strongly associated with the development of bacterial keratitis and corneal perforation.

MOTS CLÉS
Lifitegrast ;
Dry eye ;
Infectious keratitis ;
Eye perforation ;
Évisceration

Résumé La maladie du greffon contre l'hôte (GVHD) est une complication courante chez les patients qui subissent une greffe de cellules souches allogéniques pour une leucémie myéloblastique aiguë dont le traitement pourrait être très difficile. Lifitegrast 5 % (Xiidra@, Novartis), une nouvelle goutte oculaire immunosuppressive, a été récemment approuvée par la FDA pour le traitement de la sécheresse oculaire sévère et est actuellement à l'étude par l'Agence européenne des médicaments. En France, lifitegrast a été autorisé par les autorités françaises pour un usage temporaire en cas de syndrome réfractaire de sécheresse oculaire résistant aux substituts lacrymaux et à la cyclosporine topique. À ce jour, des complications graves n'ont été signalées qu'exceptionnellement. Dans cet article, nous rapportons le cas d'un patient âgé de 65 ans ayant des antécédents médicaux de leucémie myéloïde aiguë (LMA) diagnostiquée en 2015 et ayant reçu une première greffe de donneur apparenté compatible. En 2019, ce patient a développé une GVH chronique impliquant la peau, la muqueuse buccale et l'œil. Malgré la prise de médicaments topiques et systémiques pendant 3 mois, le patient n'a pas signalé de soulagement des symptômes oculaires. C'est pourquoi le lifitegrast lui a été prescrit. À notre connaissance, nous signalons le premier cas de perforation de la cornée pour lequel une éviscération a été nécessaire suite à un traitement avec lifitegrast topique pour une GVH chronique. Dans le cas présenté ici, on peut supposer que les mécanismes sous-jacents menant à la perforation de la cornée sont multifactoriels. En utilisant les critères d'imputabilité des médicaments, le lifitegrast semble être fortement associé à l'apparition de kératites bactériennes et de perforations de la cornée.

Introduction

Graft-versus-host disease (GVHD) is a common complication in patients undergoing allogeneic stem cell transplantation for acute myeloblastic leukemia [1]. The underlying pathophysiology includes an alloimmune reaction between the donor lymphocytes and the host cells [2]. GVHD patients experience severe ocular dryness resulting from an infiltration of the lacrimal gland and Meibomian glands by T cells. Several studies have reported the presence of cytokines (such as interleukin 6 [IL-6] and interferon-γ) and chemokines (such as chemokine C-X-C ligands 9, 10, and 11) in tears and in the ocular surface of GVHD patients [2,3]. Recently, new inflammatory signaling pathways activated in GVHD have been reported, such as the upregulation of intercellular adhesion molecule 1 (ICAM-1) and the toll-like receptor 2 (TLR2)-mediated NF-kB pathway [4].

Acute ocular GVHD ranges from ocular dryness to severe pseudomembranous conjunctivitis [3]. Chronic ocular GVHD is characterized by chronic qualitative and quantitative dry eye syndrome [3] and is associated with an increased risk of corneal complications. Corneal perforation due to GVHD is exceedingly rare but has already been reported [4]. Local treatments include tear replacement, autologous serum tears, and immunosuppressant medications such as steroids or cyclosporine eye drops [3]. In the case of refractory corneal ulceration, amniotic membrane transplantation or tarsorrhaphy may be needed [3].

Lifitegrast ophthalmic solution 5% (Xiidra@, Novartis) is a new immunosuppressant eye drop that was approved by the FDA in July 2016 for the treatment of severe ocular dryness. Lifitegrast is currently under investigation by the European Medicines Agency (EMA). Lifitegrast has been authorized by the French authorities for temporary use in cases of dry eye syndrome refractory to tear replacement and topical cyclosporine. Lifitegrast acts by inhibiting the binding between Lymphocyte Function-associated Antigen 1 (LFA-1) and its ligand, ICAM-1). ICAM-1 is expressed by corneal and conjunctival cells and its expression is induced by inflammatory mediators such as TNF-α and IL-1. Once activated, ICAM-1 promotes T-cell migration and activates CD4+ T cells expressing LFA-1. Several pilot studies have shown the efficacy of lifitegrast in treating ocular GVHD with a good safety profile and only minor side effects [5,6]. The common side effects of lifitegrast include burning, itching and ocular redness upon instillation [7].

We herein report the first case of corneal perforation following lifitegrast eye drop administration for the treatment of chronic ocular GVHD.

The patient's consent for publication was obtained, and this study adhered to the principles outlined in the declaration of Helsinki. This study was approved by the French ophthalmology society ethics committee (IRB number: 00008855).

Case report

We report the case of a 65-year-old patient with a past medical history of acute myeloid leukemia (AML) diagnosed in 2015, who received a first matched related donor bone marrow transplantation. In October 2019, the patient developed chronic GVHD involving the skin, the oral mucosa and the eye. The patient complained of eye pain and intense photophobia. The ophthalmologic examination revealed dry eyes classified as grade 2 according to the Oxford grading scale. Artificial tears and 0.1% topical cyclosporine were initiated. Oral steroids were also initiated for treatment of his skin and mucosal involvement. Despite taking topical and systemic medications for 3 months, no relief of the ocular symptoms was reported by the patient. Therefore, topical cyclosporine was discontinued, and lifitegrast was prescribed on January 14, 2020 (day 0) by the patient's hematologist, twice daily. On day 10, the patient experienced a burning sensation in his eyes upon lifitegrast administration and thus reduced the dose to once daily on his own. On day 15, the patient complained of a red left eye and was treated with topical antibiotics and steroids (tobramycin + dexamethasone) in combination with lifitegrast. An ophthalmologic consultation was scheduled. On day 16, the patient was referred to our emergency department for unbearable left eye pain. The ophthalmologic examination showed visual acuity in the left eye reduced to light perception. Slit-lamp examination found a dense, friable corneal infiltrate complicated by dramatic corneal thinning and a narrow anterior chamber. An infectious corneal perforation was diagnosed. The patient was hospitalized, and a surgical closure of the corneal defect with conjunctival flaps was performed urgently. At the end of surgery, an intravitreal injection of vancomycin and ceftazidime was administered to prevent bacterial endophthalmitis. Lifitegrast and steroid eye drops were discontinued and replaced by ceftazidime and vancomycin eye drops for 15 days. Bacteriological sample testing identified multisensitive Staphylococcus aureus. The early postoperative course was uneventful. On day 36, the patient returned to the hospital for excessive left eye bleeding. Examination and ultrasonography B-scan showed spontaneous expulsive hemorrhage due to reopening of the conjunctival flap (Fig. 1A). No associated intraocular infection was noted. The left eye was eviscerated on day 40. No intraocular infection was noted intraoperatively (Fig. 1B). Evisceration with a split-sclera technique was performed allowing placing a 20-mm porous orbital implant (Fig. 1C and D). Intraoperative bacteriological samples were sterile. The patient was discharged on day 42. On day 70, the follow-up examination showed no evidence of socket infection, implant exposure or fornix foreshortening. An ocular prosthesis was delivered at six weeks postoperatively and provided a favorable cosmetic result (Fig. 2).

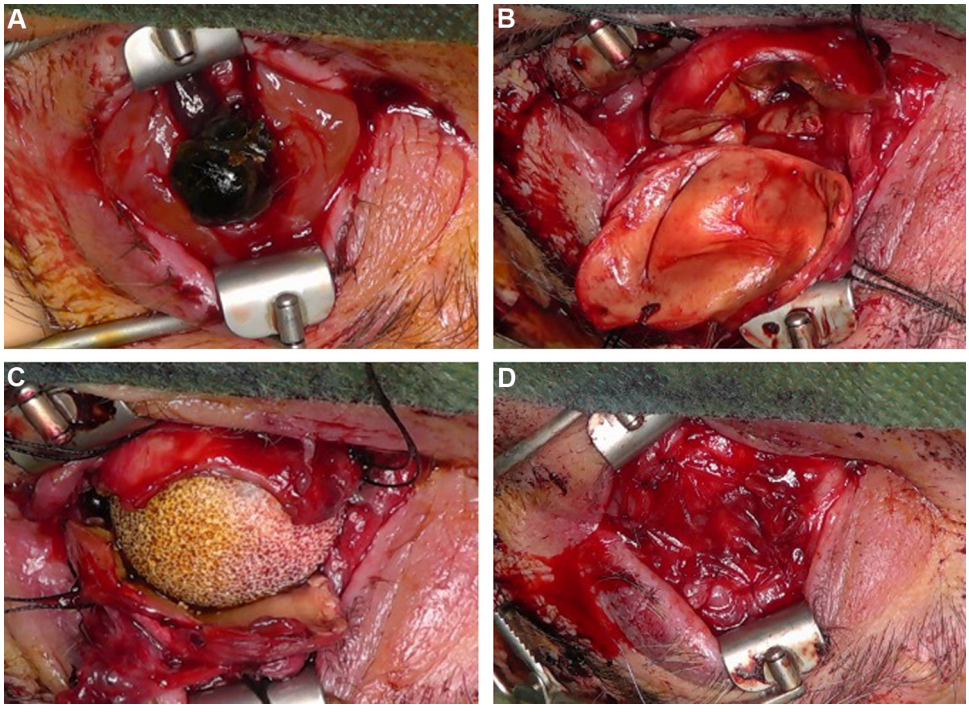

Figure 1. Intraoperative findings. A. Reopening of the conjunctival flaps complicated by expulsive choroidal hemorrhage. B. Evisceration with a split-sclera technique was performed. No intraocular infection was noted intraoperatively. C. Reconstruction of the anophthalmic cavity by placement of a 20-mm bioceramic implant. D. Socket appearance at the conclusion of surgery.

Table 1 Summary of studies assessing the efficacy and safety profile of Lifitegrast. DED: Dry Eye Disease.

Study, year	Design	Number of patients	Mean age (years)	Indications: number (%)		Side effects: number (%)	Follow-up (days)
					Ophthalmological	Systemic	
Tong et al. 2020	Retrospective	121	60.5	DED	Burning/irritation/staining: 24 (19.8) Blurry vision: 7 (5.8) Redness: 6 (4.9) Itching: 4 (3.3) Watering: 3 (2.4) Worsening: 1 (0.8) Increased sensitivity 1 (0.8) Increased blinking: 1 (0.8) Eyelid tingling: 1 (0.8)	Headache: 1 (0.8) Dysgeusia: 1 (0.8)	210
Nichols et al., 2019	Prospective randomized	2464	59.4	DED	Instillation site irritation: 195 (15.2) Blurred/blurry vision upon instillation, ocular discharge, or ocular pressure sensation upon instillation: 158 (12.3) Instillation site pain: 126 (9.8)	Dysgeusia: 186 (14.5)	NR
Chhabra et al., 2019	Retrospective	18	NR	GVHD	Allergy: 1 (5.55) Pain: 2 (11.1)	None	100
Atallah et al., 2019	Retrospective	168	NR	DED	Blurry vision: 16 (9.5) Burning: 13 (7) Instillation site reaction: 11 (6.5) Eye irritation: 12 (7) Transient redness: 14 (8.3) Eye discomfort: 12 (7) Eye Irritation: 12 (7)	Dysgeusia: 16 (9.5)	180
Tauber et al., 2015	Prospective randomized	718	58.8	DED	Reduced visual acuity: 18 (5.0) Instillation site irritation: 28 (7.8) Instillation site reaction: 25 (7.0)	Dysgeusia: 58 (16.2)	84

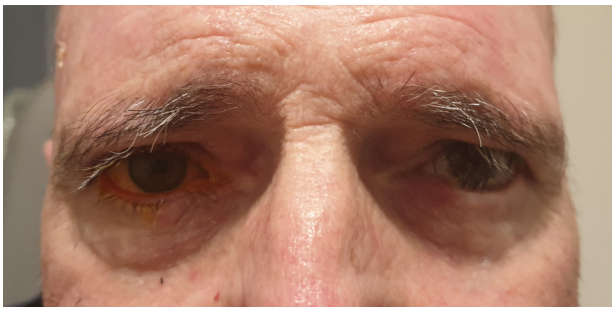

Figure 2. 6-month postoperative result with ocular prosthesis.

Discussion

To our knowledge, we report the first case of corneal perforation for which evisceration was required following treatment with topical lifitegrast for chronic ocular GVHD. Chronic ocular GVHD is a common immunological disorder secondary to bone marrow transplantation. Ocular GVHD may occur in 40—60% of allografted patients [3].

Lifitegrast is a new FDA-approved topical medication used for the treatment of dry eye syndrome. Lifitegrast blocks the interaction between LFA-1 and ICAM-1. Lifitegrast has been associated with favorable results in the treatment of dry eye disease [6,7], including ocular GVHD. The side effects of lifitegrast have been investigated in several phase 2 and 3 pilot studies, which are summarized in Table 1. The most common side effects are benign and include ocular irritation, burning and redness. Blurred vision may be found in up to 10% of patients [7]. Systemic side effects such as dysgeusia have been reported in up to 16% of patients [7].

To our knowledge, serious side effects such as corneal perforation have rarely been reported, and none of these cases required evisceration or enucleation. In the case presented herein, it can be assumed that the underlying mechanisms leading to corneal perforation were multifactorial.

Ocular GVHD has rarely been associated with spontaneous corneal perforation [8]. In our case, we do not feel that the natural evolution of ocular GVHD could have promoted the ocular perforation, since the last ophthalmologic consultation before the lifitegrast was prescribed identified only grade 2 dry eye according to the Oxford grading scale.

Topical 0.1% cyclosporine might have promoted ocular surface immunosuppression. Cyclosporine, through its action on calcineurin, inhibits T-cell proliferation and differentiation and reduces cytokine production, in particular IL-2, IL-4, IL-5, and interferon-γ). In our case, topical cyclosporine was discontinued when topical lifitegrast was initiated. The residual concentration of cyclosporine as well as its residual effect are difficult to assess. The ocular pharmacokinetics of cyclosporine have not been investigated. The plasma half-life of cyclosporine is approximately 19 hours; therefore, a washout period of 6 days is necessary for its elimination. Topical cyclosporine has been used in ophthalmology for over 30 years. Its ocular safety profile is very well known, and no serious adverse effects have been reported [9]. The potential infectious risk of topical cyclosporine (Ikervis) outlined in the EMA risk management plan is considered low. According to the international drug safety database, 38 cases of keratitis, including 23 cases of severe keratitis, have been reported with cyclosporine eye drops over a 30-year period. In our case, topical cyclosporine was prescribed at a very low dose (0.1%).

Although they were prescribed for less than 24 hours and in combination with antibiotics, topical steroids probably worsened the ocular surface infection. Steroids inhibit phospholipase A2 and reduce the recruitment of macrophages,

Table 2 Summary of imputability criteria leading to corneal perforation.

Imputability criteria	Lifitegrast	Cyclosporine	Topical Steroids	GvHD
Chronological				
Onset	Perforation occurred 15 days after initiation	Discontinued 14 days before perforation	Perforation 1 day after initiation	Perforation occurred 4 months after the first symptoms of GVHD
Evolution	Worsening	Stable	Worsening	Clinical improvement of GVHD
Semiological				
Clinical involvement	Burning Photophobia Pain	Burning Photophobia Pain	Burning Photophobia Pain	Burning Photophobia Pain
Bilbiographic				
Published International pharmacovigilance database	Yes 34 cases of ulcerative keratitis FDA approval since 2016	Yes 16 cases of ulcerative keratitis 30-year follow-up	Yes (20)	None

polynuclear cells and lymphocytes[10]. Systemic and local steroids could have played a role, but the time between their initiation and the occurrence of the corneal perforation (less than 24 hours) does not suggest direct toxicity.

In the case presented herein, we believe that lifitegrast led to the corneal infection and perforation. We consulted the World Health Organization Safety Database, Vigibase®, and extracted data using Vigilyze®, and we recorded up to 150 cases of ocular infections related to lifitegrast eye drops as of April 2020. In this database, lifitegrast was prescribed for ocular dryness. Of the 150 reported cases, 86 were classified as serious and included 53 cases of keratitis, 34 cases of ulcerative keratitis, 1 case of corneal perforation (unknown management) and 1 case of blindness (without further details). Using the drug imputability criteria summarized in Table 2, lifitegrast appears to be strongly associated with the occurrence of bacterial keratitis and corneal perforation. The timing of the symptoms of this ocular perforation are very likely to be related to the initiation of lifitegrast.

To conclude, ophthalmologists as well as hematologists should be aware of the possible serious side effects of lifitegrast. Lifitegrast should be prescribed with caution. We recommend the prescription of lifitegrast by an ophthalmologist after discussion with the bone marrow transplantation specialist as well as the discontinuation of other topical immunosuppressant medications before its use.

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None.

Disclosure of interest

The authors declare that they have no competing interest.

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