Journal of Chemotherapy

ISSN: 1120-009X (Print) 1973-9478 (Online) Journal homepage: http://www.tandfonline.com/loi/yjoc20

Does topical voriconazole trigger dysplastic changes on the ocular surface?

Melis Palamar, Sait Egrilmez, Suzan Guven Yilmaz, Suleyha Hilmioglu Polat & Omur Ucakhan Gunduz

To cite this article: Melis Palamar, Sait Egrilmez, Suzan Guven Yilmaz, Suleyha Hilmioglu Polat & Omur Ucakhan Gunduz (2015) Does topical voriconazole trigger dysplastic changes on the ocular surface?, Journal of Chemotherapy, 27:2, 111-113, DOI: 10.1179/1973947814Y.0000000166

To link to this article: http://dx.doi.org/10.1179/1973947814Y.0000000166

Published online: 28 Jan 2014.

Case Report

Does topical voriconazole trigger dysplastic changes on the ocular surface?

Melis Palamar[1], Sait Egrilmez[1], Suzan Guven Yilmaz[1], Suleyha Hilmioglu Polat[2], Omur Ucakhan Gunduz[3]

[1]Ege University Faculty of Medicine, Department of Ophthalmology, Izmir, Turkey, [2]Ege University Faculty of Medicine, Department of Microbiology, Izmir, Turkey, [3]Ankara University Faculty of Medicine, Department of Ophthalmology, Turkey

Purpose: Systemic voriconazole treatment was reported to cause photosensitivity and related cutaneous malignancies. The aim of this report is to demonstrate a graft-related Candida endophthalmitis case that developed ocular surface dysplastic changes after receiving topical 1% voriconazole treatment.
Methods: Full ocular examination, photography, and *in vivo* confocal microscopy examination (Rostock Cornea Module/HRT II, Heidelberg, Germany) were performed.
Results: A 73-year-old male with graft-related Candida endophthalmitis that was on topical 1% voriconazole for 4 months developed a whitish gelatinous lesion on the cornea originating from the nasal limbus. *In vivo* confocal microscopy examination revealed mild dysplastic changes in the cornea epithelium.
Conclusion: Topical voriconazole might trigger neoplastic changes on the ocular surface as reported with systemic use in other sun-exposed parts of the body. Further studies are needed to relate topical use of voriconazole with ocular surface dysplasia.

Keywords: Candida, Confocal microscopy, Cornea, Dysplasia, Penetrating keratoplasty, Voriconazole

Fungal endophthalmitis can be exogenous (trauma, surgery, and contiguous spread from ocular infection) or endogenous in origin, and treatment options are limited.[1] Voriconazole – a second-generation triazole used initially as prophylaxis for invasive fungal infections in patients with haematological malignancies or stem cell transplants – was reported to achieve therapeutic aqueous concentrations even in non-inflamed human eyes when used topically.[2] Thus, its activity spectrum seems to appropriately include the most frequently encountered mycotic species causing keratitis and endophthalmitis. However, phototoxicity and cutaneous malignancies due to systemic voriconazole use have been reported.[3–5]

This report is a case of graft-related Candida endophthalmitis that developed ocular surface dysplastic changes after receiving topical 1% voriconazole treatment for 4 months.

Case Report

A 73-year-old male with history of keratitis in the left eye underwent uneventful penetrating keratoplasty for corneal scarring. Postoperatively, he was put on topical tobramycin and dexamethasone. On the postoperative fourth day severe anterior chamber reaction and hypopyon with accompanying mucopurulent discharge were detected. Upon microbiological evaluation of aqueous humour, Candida parapsilosis was detected and the microorganism was found to be highly sensitive to voriconazole. With co-existent vitreous involvement on ultrasonography, the patient was diagnosed as graft-related Candida endophthalmitis; 1% voriconazole was injected intracamerally and topical 1% voriconazole drops were started, and 1% voriconazole was injected intravitreally to combat intraocular infection. The infection was successfully controlled with this therapy regimen; however, as reported in the literature, the application of 1% voriconazole eye drops was decided to be continued for 6 months QID.

During a routine examination in the fourth month of therapy, a whitish gelatinous lesion on the cornea originating from the nasal limbus was detected (Fig. 1). *In vivo* confocal microscopy examination (Rostock Cornea Module/HRT II, Heidelberg, Germany) revealed mild dysplastic changes in the cornea epithelium (Fig. 2 A–C). A scraping biopsy was performed to confirm the lesion. However, due to insufficient specimen, dysplastic changes could not be histopathologically

Correspondence to: Melis Palamar, Ege Universitesi Tip Fakultesi Goz Hastaliklari AD, 35040 Bornova, Izmir, Turkey. Email: melispalamar@hotmail.com

DOI 10.1179/1973947814Y.0000000166

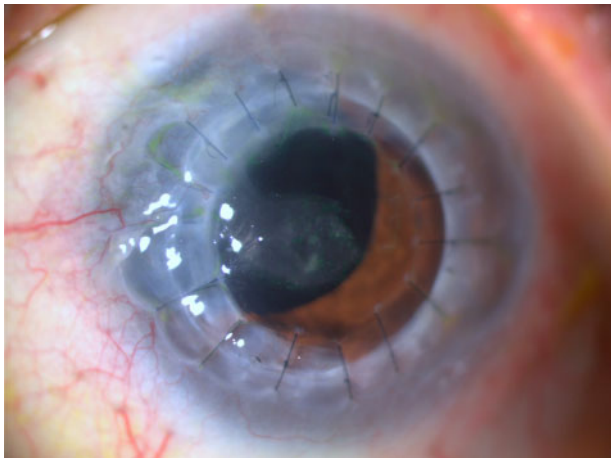

Figure 1 Whitish gelatinous corneal lesion originating from the nasal limbus is evident.

proven. Topical interferon alpha2b (1 million units/ml four times daily) was administered for 3 months in order to eliminate any residual tumour cells. At the time of submission, the patient and graft had been healthy for a total of 18 months after the cessation of interferon therapy.

Discussion

Voriconazole is an extended-spectrum triazole antifungal approved for treatment of invasive fungal infections.[2] *In vitro* studies have shown voriconazole to have a broad spectrum of action against many microorganisms.[2] The drug exerts its effect by binding and inhibiting cytochrome P450-dependent lanosterol 14-alpha-demethylase, an enzyme used for the synthesis of ergosterol, an essential lipid constituent of the cell membranes of fungi. Exposure to the drug leads to depletion of ergosterol and inhibition of fungal cell growth and replication.[2] Drug-induced phototoxicity and malignancies such as cutaneous melanoma and squamous cell carcinoma have been reported to be associated with this medication in long-term systemic therapy.[3–5]

Ocular surface squamous neoplasia (OSSN) encompasses a broad spectrum of neoplastic squamous epithelial abnormalities, including squamous dysplasia, squamous cell carcinoma *in situ*, and invasive squamous cell carcinoma.[6] These neoplastic conditions can affect the conjunctiva as well as the corneal surface. The proposed aetiologic risk factors for OSSN include environmental exposure to UV-B solar radiation, cigarette smoke, human papilloma virus (HPV), human immunodeficiency virus (HIV), petroleum products, medical immunosuppressive agents for organ transplant, and corneal graft.[6]

Confocal microscopy obtains *in vivo* high-resolution optical images of human corneal layers and conjunctiva. The key features of confocal microscopy are its ability to produce in-focus images of thin slices (5–20 mm) within a maximum depth of 1000 mm, a process known as optical sectioning. The utilization of this technique in the diagnosis of OSSN has been reported.[7,8] Gentile *et al.*[8] reported seven eyes affected by corneal intraepithelial neoplasia, documenting pleomorphic, medium sized, hyper-reflective nucleated cells with indistinct cytoplasmic border, and with a sharp transition between neoplastic and non-neoplastic epithelium.

The patient in this case had no history of working outdoors, smoking, receiving systemic immunosuppressive treatment, or having HPV or HIV infection. However, penetrating keratoplasty and topical corticosteroid use were risk factors. Although unconfirmed by the biopsy, confocal microscopy revealed pleomorphic, medium-sized, hyper-reflective nucleated cells with indistinct cytoplasmic borders, similar to those detected by Gentile *et al.*,[8] suggesting a

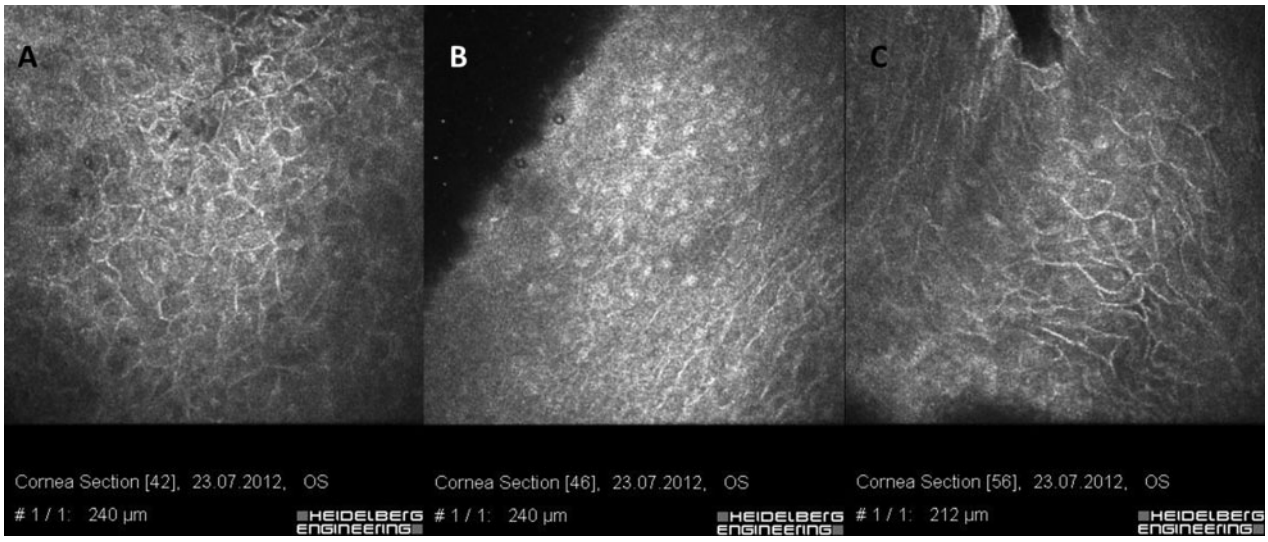

Figure 2 Representative pictures from in vivo confocal microscopy. (A) Epithelial cells were enlarged, irregular, and pleomorphic in shape. (B) On horizontal sections enlarged nuclei with high nuclear to cytoplasmic ratio, highly reflective cytoplasm, and indistinct cytoplasmic borders were detected. (C) Epithelial cellular anisocytosis and anisonucleosis were evident.

diagnosis of OSSN. As it is known that fungal corneal ulcers might heal with hyperplastic masses or fibrous sheets in the region of healing lesions, one can wonder if these corneal lesions might be related to the Candida keratitis.[9] However, the corneal graft in this patient was clear for at least 4 months prior to development of this dysplastic lesion which supports that it occurred due to voriconazole treatment.

A literature review of topical voriconazole use and OSSN revealed no results. We report this case in order to draw attention to the potential of this medication to trigger neoplastic changes on the ocular surface as reported with systemic use in other sun-exposed parts of the body. However, further studies are needed to relate topical use of voriconazole with OSSN. Ocular photoprotection, as suggested in systemic drug use,[3–5] can prevent the development of probable sun-induced ocular surface problems, allowing patients to continue taking voriconazole for prophylaxis against or management of topical fungal infections.

Disclaimer Statements

Contributors Melis Palamar: research, analysis and manuscript preparation. Sait Egrilmez, Suzan Guven Yilmaz, Suleyha Hilmioglu Polat and Omur Ucakhan Gunduz: Analysis.

Funding None.

Conflicts of interest None.

Ethics approval This is a retrospective case presentation, and informed consent was received.

References

1 Vemulakonda GA, Hariprasad SM, Mieler WF, Prince RA, Shah GK, Van Gelder RN. Aqueous and vitreous concentrations following topical administration of 1% voriconazole in humans. Arch Ophthalmol. 2008;126:18–22.
2 De Sarro A, La Camera E, Fera MT. New and investigational triazole agents for the treatment of invasive fungal infections. J Chemother. 2008;20:661–1.
3 Vöhringer S, Schrum J, Ott H, Höger PH. Severe phototoxicity associated with long-term voriconazole treatment. J Dtsch Dermatol Ges. 2011:9(4):274–6.
4 Cowen EW, Nguyen JC, Miller DD, McShane D, Arron ST, Prose NS, *et al.* Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. J Am Acad Dermatol. 2010;62:31–7.
5 Miller DD, Cowen EW, Nguyen JC, McCalmont TH, Fox LP. Melanoma associated with long-term voriconazole therapy: a new manifestation of chronic photosensitivity. Arch Dermatol. 2010;146:300–4.
6 Kiire CA, Srinivasan S, Karp CL. Ocular surface squamous neoplasia. Int Ophthalmol Clin. 2010;50:35–46.
7 Parrozzani R, Lazzarini D, Dario A, Midena E. *In vivo* confocal microscopy of ocular surface squamous neoplasia. Eye. 2011;25:455–60.
8 Gentile CM, Croxatto JO. *In vivo* diagnosis of epithelial neoplastic changes of the cornea and conjunctival limbus using confocal microscopy. Invest Ophthalmol Vis Sci. 2008;49:E-5680.
9 Srinivasan M. Fungal keratitis. Curr Opin Ophthalmol. 2004;15:321–7.