An unusual case of bluish discoloration of the cornea after favipiravir therapy for COVID-19

Dear Editor,

A 20-year-old male presented to the Physician with symptoms of fever, cough, and malaise for 5 days. A nasopharyngeal swab was subjected to reverse transcription-polymerase chain reaction and was found to be positive for the SARS-CoV-2 virus. He was started on oral vitamin C 500 mg TDS, zinc 60 mg OD, vitamin A single dose, and vitamin D single dose. He was also started on oral ivermectin 12 mg OD. The patient did not show any improvement after 2 days of treatment, and had persistence of fever and worsening of cough with excessive sputum production. He was then started on favipiravir therapy. He received 1600 mg favipiravir BD on day 1 and the morning dose of 800 mg favipiravir on day 2, when he noticed bluish discoloration of his eyes [Fig. 1]. There was no blurring of vision and the recorded visual acuity was 20/20. Slit-lamp examination revealed bluish corneal hue. There were no pigment deposits visible, no evidence of corneal thickening or fluorescence on cobalt blue filter. The lens and anterior chamber appeared normal with clear anterior chamber contents. Gonioscopy revealed normal angles with no abnormal trabecular meshwork pigmentation and intraocular pressures of 10 and 12 on Goldmann applanation tonometer. There was no bluish discoloration of any other areas such as skin, nails, or oral and nasal mucosa. The patient also produced his old photographs wherein the color of his corneas was perfectly normal. We assumed that the bluish corneal hue could be related to favipiravir and advised the patient to stop using favipiravir immediately. It was remarkable to note that the very next day upon stopping favipiravir the patient’s corneas returned to normal color [Fig. 2].

Favipiravir is currently approved for usage in mild to moderate COVID-19 in India. The SARS-CoV-2-RdRp complex is 10 times more active than any other known RdRp complex. Favipiravir, an antiviral agent, acts by inhibiting this viral RdRp enzyme thus allowing favipiravir to insert into the viral RNA and sparing the human DNA. In this way, it prevents the further extension of the viral RNA strand. It has also been seen that favipiravir induces lethal mutagenesis in influenza A virus in vitro. A similar response is expected with SARS-CoV-2 virus. The currently used dose in most countries including India is 1800 mg BD on day 1 followed by 800 mg BD on days 2–14.\[1\]

A Japanese study by James\[2\] using favipiravir in COVID-19 patients reported adverse effects in about 20% of the participants who received favipiravir. These included mild hyperuricemia, diarrhea, and neutropenia. Few individuals also showed prolongation of QT interval on an electrocardiogram.\[3\] There have also been case reports where fluorescence of hair and nails when seen under Wood’s lamp after treatment with favipiravir was reported.\[4\] Recently in April 2021 Doran et al.\[5\] reported a case where a 20-year-old photographer who was started on favipiravir presented on the second day of therapy with blurred vision and blue light reflection when he was exposed to UV light sources at his workplace. On examination, they noticed fluorescence of his corneas and nails under Wood’s lamp, but no bluish discoloration of cornea was noted and slit-lamp biomicroscopy was not significant. There is no other such case of bluish discoloration of the cornea that we could find in the literature despite extensive literature search. Hence, ours is the first case of bluish discoloration of the corneas after favipiravir therapy to be reported. The fluorescence and bluish corneal hue could be a result of the drug favipiravir or its metabolites itself or other ingredients such as titanium dioxide and yellow ferric oxide.\[6\] However, the drug’s active metabolite in the phosphorylated form was found by Megahed et al.\[7\] in human plasma and its plasma concentration and fluorescence intensity showed a linear relationship. The same could be applied to the cornea. Favipiravir has a high absorption rate of ~97.6% and a plasma protein binding of 54%. High doses of this phosphorylated active metabolite of favipiravir achieving high concentrations in the plasma after favipiravir intake and consecutively appearing in the aqueous humor after systemic administration may be responsible for its absorption or a mere reflection in the cornea leading to a bluish hue and fluorescence. The aqueous humor being an ultrafiltrate of plasma, the plasma constituents have a direct association with the nature of aqueous humor. However, the exact mechanism needs to be further studied by further investigations such as aqueous tap and analyzing the aqueous humor and its constituents.

Conclusion

The appearance of bluish corneal hue on the second day of favipiravir therapy and its immediate disappearance with return of normal corneal color directly points toward the fact that the bluish discoloration of the corneas was a result of favipiravir. Also, despite extensive literature search, we could not find any case of bluish discoloration of the corneas. Hence, we report the first such case of bluish discoloration of corneas after treatment with favipiravir.

Figure 1: Bluish discoloration of both cornea while patient is on favipiravir therapy

Figure 2: Both cornea are seen to return to normal color after cessation of favipiravir therapy
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Cite this article as: Raiturcar TP, Nayak CA. An unusual case of bluish discoloration of the cornea after favipiravir therapy for COVID-19. Indian J Ophthalmol 2021;69:3778-9.