

## REVIEW

# Dilemmas of recurrent ocular inflammatory disease on immunosuppression and corona virus disease vaccination

Srinivasan Sanjay<sup>1\*</sup>, Sathi Devi<sup>2</sup>, Sharath Kumar<sup>3</sup>, Ankush Kawali<sup>4</sup>, Padmamalini Mahendradas<sup>5</sup>

<sup>1, 4,5</sup> Department of Uveitis and Ocular immunology, Narayana Nethralaya, Bangalore, India

<sup>2</sup>Department of Glaucoma, Narayana Nethralaya, Bangalore, India

<sup>3</sup>Optima Arthritis and Rheumatology Clinic, Bangalore, India

## Abstract

The current study explores the occurrence of ophthalmic manifestations following coronavirus disease-19 (COVID-19) vaccination. The study discusses the case of a 72-year-old Indian male, who received oral methotrexate for ocular inflammation (recurrent post-operative uveitis with pseudoexfoliative glaucoma) and two doses of COVISHIELD™ vaccine and a booster in 2022. While he discontinued methotrexate for 2 weeks after the first dose, he continued the medication during the second and booster doses. Subsequently, he experienced mild ocular inflammation two weeks after the first dose, one day after the second dose, and one week after the booster dose. Topical steroids effectively controlled the inflammation, and an increased oral methotrexate dosage was used after the second dose. The study highlights the potential for autoimmune inflammatory syndrome following vaccination, although a definite causal link cannot be established. Nonetheless, the presence of side effects should not discourage individuals from receiving vaccinations.

Keywords: coronaovirus, COVID, anterior uveitis

## Introduction

Ophthalmic manifestations have been reported following coronavirus disease (COVID-19) vaccine including episcleritis, scleritis, recurrent anterior uveitis, multifocal choroiditis, acute macular neuroretinopathy, paracentral acute middle maculopathy, vein occlusion, Vogt-Koyanagi-Harada disease (VKH), central serous chorioretinopathy (CSCR), herpes zoster re-activation or acute retinal necrosis.<sup>1-15</sup> There are also reports of anterior uveitis occurring following 1st or 2nd dose of COVID-19 vaccination.<sup>1,9</sup> The current study discusses the case of a patient with recurrence of intraocular inflammation after COVID-19 vaccine after both first and second doses, and subsequently following the booster dose.

## Case report

A 72-year-old Asian Indian male presented with pain and redness in his left eye (OS) for a duration of one week. He was receiving treatment for type 2 diabetes mellitus and gout. His ocular history revealed undergoing cataract surgery in both eyes (OU) in 2005 with multifocal intraocular implantation.

In 2019, he experienced left lateral rectus palsy and had completely recovered. MRI of the brain and orbit (plain and contrast) during that episode showed chronic small vessel ischemia. He had undergone treatment with oral steroids starting at 30 mg in a tapering dose for the lateral rectus palsy.

Ophthalmic evaluation conducted in June 2020 showed a best-corrected visual acuity (BCVA) of 20/20 in OU and intraocular pressure (IOP) of 18/28 mm Hg in the right eye (OD) and OS, respectively. The OS exhibited superior decentration of the intraocular lens in the sulcus with pseudophacodonesis and pseudoexfoliative (PXF) material in the angle and on the lens capsule. Gonioscopy revealed open angles with dense pigmentation of the trabecular meshwork in OU. Additionally, the OS had a cup-disc ratio of 0.8 with inferotemporal rim thinning and disc pallor, along with corresponding advanced field defects (bi-arcuate scotoma with tubular sparing). The examination of OD was normal, except for pseudoexfoliative material on the capsule and in the angle. Travoprost 0.004% eye drops were started

in OS to control IOP.

In October 2020, he presented with pain and redness in OS. Ophthalmic evaluation showed a BCVA of 6/8 in OD and counting fingers close to the face in OS. IOP in the OS was 24 mm Hg. The left eye evaluation showed circumciliary congestion, corneal epithelial bullae, corneal stromal edema, endothelial pigments, 1 mm hyphema, and 2+ flare and cells in the anterior chamber. Due to his corneal involvement, there was no view of the fundus. An ultrasound B-scan of the OS showed a few vitreous debris with optic nerve cupping, and retinochoroidal thickening was measured at 1.26 mm, which was within normal limits. A diagnosis of recurrent post-operative uveitis with pre-existing glaucoma was considered. Specifically, this patient was diagnosed with uveitis-glaucoma-hyphema (UGH) syndrome in the OS. Herpetic anterior uveitis was considered in the differential diagnosis but was deemed an unlikely cause, as the patient's history of PXF, pseudophacodonesis, and diffuse endothelial pigments were not in its favor.

Topical brimonidine and travoprost were stopped due to the presence of ocular inflammation. Instead, the patient was started on brinzolamide (1%) + timolol (0.5%) eye drops, and oral acetazolamide 125 mg four times a day, as the patient was intolerant to the full oral dose of 250 mg. He was reviewed at the uvea clinic on the same day and began using prednisolone acetate 1% eye drops four times a day and bromfenac 0.09% eye drops thrice daily for the OS. A week later, ophthalmic evaluation showed a BCVA of 6/6 in the OD and hand motion in OS. His IOP in the OS was 28 mm Hg. To address inflammation, he was started on oral steroids at a dose of 35 mg (0.5 mg/kg/bodyweight) in an anti-inflammatory regimen. The IOP noted in the following week was 22/44 mm Hg in OD/OS, respectively, as the patient was a steroid responder. The patient agreed to and proceeded with the option of Ahmed glaucoma valve for further management.

His post-operative condition was uneventful, with a good bleb, and oral steroids were tapered. One month after surgery, there was no inflammation, but the IOP had increased to 30 mm Hg in OD and 26 mm Hg in OS. The option of intraocular lens exchange was considered, but the patient was not keen on further surgical intervention and alternative medical management was sought.

Steroid-sparing immunosuppressive treatment, consisting of oral methotrexate 15 mg/week along with oral folic acid 5

mg, was initiated by the rheumatologist and continued for a month. His eye pressures were measured at 20 mm Hg in OD and 14 mm Hg in OS with no evidence of inflammation. After five weeks of starting the immunosuppressive treatment, the patient received the COVISHIELD™ vaccination. The treating rheumatologist discussed the advantages and disadvantages of interrupting methotrexate to improve vaccine effectiveness, following available clinical guidance.<sup>10</sup> Subsequently, the patient chose to suspend immunosuppression for 2 doses of the vaccine.

The points to ponder here are as follows:

- Should immunosuppression have been stopped?
- Was stopping immunosuppression the cause of reactivation?
- Did the vaccination trigger the immune response leading to inflammation?

In the second/third instance of vaccine administration, there was a definite recurrence of anterior chamber inflammation following vaccination, despite being on immunosuppression.

### **Search strategy**

To explore the possibility of similar cases of anterior uveitis reported in indexed journals, we used the Medical Subject Headings (MeSH) of MEDLINE with the terms 'Uveitis', 'Anterior,' 'COVID-19,' and 'Ocular Inflammation.' In January 2022, the search yielded 21 articles in English, out of which 6 articles containing data on anterior uveitis and COVID-19 vaccination were included for analysis.

Table 1 summarizes the cases that presented with AU following COVID-19 vaccination. It also includes two updated references of cases published in 2023.

### **Discussion**

The current study presents the case of a patient with UGH syndrome and recurrent post-operative inflammation. The patient's disease was well-controlled on methotrexate, but it flared up after receiving the COVISHIELD™ vaccine. In an attempt to potentially improve vaccine uptake and efficacy, the patient skipped 2 doses of methotrexate. However, he developed ocular inflammation twice during the next 2 doses of the vaccine.

There is no clinical data available for patients with autoimmune conditions regarding the safety and efficacy of COVID-19 vaccines. Therefore, most expert bodies recommend that patients with autoimmune diseases should consider the heightened risk of infections and possibly poorer

**Table 1: Summary of cases that presented as anterior uveitis after COVID-19 vaccination**

Author	Number of patients	Symptoms after vaccine	COVID vaccine type	1st/ 2nd dose/ both (number of patients)	Type of anterior uveitis (number of patients)
Sanjay et al. <sup>10</sup>	1	7-29	*COVISHIELD	1 <sup>st</sup> (29) 2 <sup>nd</sup> (7)	Non-granulomatous
Sanjay et al. <sup>11</sup>	1 HLA- B27 positive	7	*Covaxin	2 <sup>nd</sup> (7)	Non-granulomatous
Testi et al. <sup>28</sup>	41	1-14	*Pfizer *Astra-Zeneca *Moderna *Sinopharm * Covaxin	1 <sup>st</sup> (22)/2 <sup>nd</sup> dose (19)	*HLA- B27 (9) *idiopathic anterior uveitis (6) *glaucomatocyclitic crisis (3) *herpetic anterior uveitis(2) *juvenile idiopathic arthritis associated uveitis (1) *CMV uveitis (1) *SLE uveitis (1)
Rabinovitch et al. <sup>29</sup>	21			1 <sup>st</sup> dose (8) 2 <sup>nd</sup> dose (13)	
Ng et al. <sup>30</sup>	7	1 day-1 month	the BNT162b2 or mRNA-1273	1 <sup>st</sup> / 2 <sup>nd</sup>	Non-granulomatous
Bolletta et al. <sup>31</sup>	5 3 were HLA- B27 positive	1-30 days	BNT162b2 mRNA-1273 ChAdOx1 nCoV-19	1 <sup>st</sup> (2)/2 <sup>nd</sup> dose (3)	4 non-granulomatous and 1 CMV AU
El Sheikh et al. <sup>32</sup>	1 ANA positive oligoarticular JIA)	5 days	Sinopharm	2 <sup>nd</sup> dose	Non-granulomatous
Renisi et al. <sup>33</sup>	1	14 days	BNT162b2	2 <sup>nd</sup> dose	Non- granulomatous

Abbreviations: HLA- B27- Human leucocyte antigen B27; Cytomegalovirus (CMV); SLE- Systemic lupus erythematosus; ANA- antinuclear antibody

outcomes while receiving COVID-19 vaccination.<sup>16-19</sup> The risk of death due to COVID-19 appears to be elevated among patients with autoimmune diseases, especially in those currently using certain immunosuppressant medications and glucocorticoids. However, this risk is predominantly related to increased age and comorbid conditions, which are overrepresented among patients with autoimmune diseases.<sup>19</sup>

The American College of Rheumatology (ACR) guidance recommends interrupting the dose of methotrexate after

vaccination to potentially improve the efficacy of the vaccination. In the current patient, it can be argued that the interruption of methotrexate precipitated the flare of the disease. It is important to note that the ACR guidance to stop methotrexate post-vaccination is possibly based on data extrapolated from a completely different type of vaccination (killed subunit vaccine of influenza) and a different disease (influenza).<sup>20</sup> The only guidance available for autoimmune eye disease is a commentary by Chau et al. and it does not suggest any break in the medications but advises doctors to use it judiciously.<sup>21</sup> Clinicians should, therefore,

consider the principle of “Primum non nocere” (First, do no harm) and exercise extreme clinical discretion, avoiding advising a break in methotrexate for patients with even the slightest possibility of a disease flare. To its credit, the ACR guidance does mention that such interruption should only be considered for those with well-controlled disease.

The current patient experienced a flare-up of disease after skipping 2 doses of methotrexate. Considering the pharmacokinetics and duration of the anti-inflammatory action of methotrexate, it is unlikely that such a short period could precipitate a disease flare. The only other potential precipitant of the flare was the COVISHIELD™ vaccination. Regarding other adult vaccinations, initial concerns about the possibility of flare-ups of rheumatological or autoimmune diseases post-vaccination were eased by findings from large cohort studies and systematic reviews.<sup>21</sup>

It is important to note that COVID-19 infection is slightly different compared to other infections in its tendency to predispose to autoimmune manifestations (both clinical and sub-clinical, i.e., autoantibodies).<sup>22</sup> Some recent scientific breakthroughs have been utilized in the race to develop a coronavirus vaccine. COVISHIELD™, an adenoviral vector vaccine, is the first viral vector vaccine to be utilized at such a large scale.<sup>23</sup> The guidelines and guidance mentioned previously do acknowledge the lack of safety data with respect to these particular vaccines among patients with autoimmune conditions. Among normal individuals, clinical trial participants who received the COVID-19 vaccine did not show any imbalances in the occurrence of symptoms consistent with autoimmune conditions or inflammatory disorders compared to those who received the placebo.<sup>24</sup> However, it is still possible that COVID-19 vaccines may precipitate flares in patients who already have autoimmune diseases.

In a study by Prendecki et al, it was found that in patients receiving immunosuppression, less than a third of infection-naïve participants seroconverted, and a quarter of them had detectable T-cell responses to SARS-CoV-2. B-cell depletion at the time of vaccination was associated with failure to seroconvert, and tacrolimus therapy was associated with diminished T-cell responses.<sup>25</sup>

Shoenfeld's syndrome occurs as an autoimmune inflammatory syndrome induced by adjuvants (ASIA) in vaccines.<sup>26</sup> ASIA may occur in patients with a personal or family history of autoimmune disease. It is essential

to inquire about any recent history of vaccination when evaluating ocular inflammation. In the current case, there was no predisposition or pre-existing autoimmune disease. In 2020, over 300 patients with intraocular inflammation were reported in the literature.<sup>27</sup> In the last one and a half years, more cases have been attributed to the COVID-19 vaccine, although it is not the cause.

## Conclusion

Mere presence of an ocular adverse effect should not discourage individuals from receiving vaccination against COVID-19. Currently, there are no specific guidelines for managing patients with ocular inflammation who are on immunosuppression. The current study proposes that immunosuppression should be continued in patients until more data emerges about the potential benefits of interrupting medications after COVID-19 vaccination. This approach may be particularly crucial for patients who have experienced recent active disease or flare-ups (within the last 3 months). While it is possible that continuing immunosuppression may reduce the vaccine's immunogenicity, this concern remains theoretical at present.

It is essential to recognize that the infection causing this pandemic is qualitatively different from other infections in two important ways. The SARS-CoV-2 virus has a propensity to induce autoimmune symptoms and autoantibodies. Therefore, clinicians and medical associations should closely monitor the possibility of these vaccines triggering flare-ups of autoimmune diseases. It is a distinct possibility that the COVISHIELD™ vaccination could have been a trigger for the current patient's flare-up of anterior chamber inflammation. However, it is essential to note that the vaccination and the anterior chamber inflammation may be a temporal event with no causal role for the vaccine.

## Conflicts of Interest

The authors declare that they have no conflict of interest.

Submitted: 28 May 2023, Accepted: 5 July 2023, Published: 31 July 2023

\*Correspondence: Dr. Srinivasan Sanjay  
sanjaygroup24@gmail.com

## Citation

Sanjay S, Devi S, Kumar S, Kawali A, Mahendradas P. Dilemmas of recurrent ocular inflammatory disease on immunosuppression and corona virus disease vaccination. *IJRCI*. 2023,11(1):R2.

DOI: 10.15305/ijrci/v11i1/378

## References

1. Pichi F, Aljneibi S, Neri P, et al. Association of Ocular Adverse Events With Inactivated COVID-19 Vaccination in Patients in Abu

- Dhabi. *JAMA Ophthalmol.* 2021 ;139:1131-1135.
2. Goyal M, Murthy SI, Annum S. Bilateral Multifocal Choroiditis following COVID-19 Vaccination. *Ocul Immunol Inflamm.*2021;29:753–7.
  3. Koong LR, Chee WK, Toh ZH, et al. Vogt-Koyanagi-Harada Disease Associated with COVID-19 mRNA Vaccine. *Ocul Immunol Inflamm.* 2021 Sep 10:1-4.
  4. Fowler N, Mendez Martinez NR, Pallares BV, et al. Acute-onset central serous retinopathy after immunization with COVID-19 mRNA vaccine. *Am J Ophthalmol Case Reports.* 2021;23:101136.
  5. Mishra SB, Mahendradas P, Kawali A, et al. Reactivation of varicella zoster infection presenting as acute retinal necrosis post COVID 19 vaccination in an Asian Indian male. *Eur J Ophthalmol.* 2021 Sep 18:11206721211046485.
  6. Sanjay S, Ponnuru D, Kumar S, et al. Herpes zoster reactivation after COVID-19 vaccination in patients with autoimmune diseases. *Indian Journal of Rheumatology* 17(2):p 216-221, June 2022
  7. Sanjay S, Gadde SGK, Kumar Yadav N, et al. "Bilateral Sequential Acute Macular Neuroretinopathy in an Asian Indian Female with  $\beta$  Thalassemia Trait following (Corona Virus Disease) COVID-19 Vaccination and Probable Recent COVID Infection- Multimodal Imaging Study.". *Ocul Immunol Inflamm.* 2022 Jan 20:1-6.
  8. Sanjay S, Kawali A, Mahendradas P. Acute macular neuroretinopathy and COVID-19 vaccination. *Indian J Ophthalmol.* 2022 Jan;70(1):345-346.
  9. Sanjay S, Kawali A. Comment on: COVID-19 vaccine-associated reactivation of uveitis. *Indian J Ophthalmol.* 2022 ;70:342-343.
  10. Sanjay S, Yathish GC, Singh Y, Kawali A, Mahendradas P, Shetty R. COVID-19 vaccination and recurrent anterior uveitis. *Indian J Ophthalmol.* 2022 Dec;70(12):4445-4448.
  11. Sanjay S, Kawali A, Mahendradas P. COVID-19 vaccination, dengue hepatitis, and recurrent unilateral anterior uveitis. *Indian J Ophthalmol.* 2023 May;71(5):2269-2272.
  12. Sanjay S, Yadav NK, Kawali A, Gupta A, Mahendradas P. Unilateral macular branch retinal vein occlusion in a healthy Indian woman following coronavirus disease vaccination: a case report and comprehensive literature review. *Med Hypothesis Discov Innov Optom.* 2023 Summer; 4(2): 95-101.
  13. Sanjay S, Handa A, Kawali A, Shetty R, Bhakti Mishra S, Mahendradas P. Scleritis and Episcleritis following Coronavirus Disease (COVID-19) Vaccination. *Ocul Immunol Inflamm.* 2023:1-7.
  14. Sanjay S, Sharief S, Gopikrishna Gadde S, Poornachandra B. Paracentral acute middle maculopathy progressing to central retinal artery occlusion following corona virus disease vaccination: a multimodal imaging report. *Med Hypothesis Discov Innov Optom.* 2023; 4(1):41-49.
  15. Sanjay S, Acharya I, Rawoof A, Shetty R. Non-arteritic anterior ischaemic optic neuropathy (NA-AION) and COVID-19 vaccination. *BMJ Case Rep.* 2022 May 13;15(5):e248415.
  16. American College of Rheumatology. COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal disease. Version 5 Revised January 28, 2022 Accessed February 1st 2022. <https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf>
  17. EULAR view-points on SARS-CoV-2 vaccination in patients with RMDs. Updated January 2021. [https://www.eular.org/eular\\_sars\\_cov\\_2\\_vaccination\\_rmd\\_patients.cfm](https://www.eular.org/eular_sars_cov_2_vaccination_rmd_patients.cfm) ( Accessed February 1st 2022)
  18. Wang Q, Liu J, Shao R, Han X, Su C, Lu W. Risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population: a systematic review and meta-analysis. *Rheumatol Int.* 2021;41:851-861.
  19. Strangfeld A, Schäfer M, Gianfrancesco MA, et al; COVID-19 Global Rheumatology Alliance. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis.* 2021 Jan 27:annrheumdis-2020-219498.
  20. Mehta P, Sanchez E, Moraitis E, et al. Influenza vaccination and interruption of methotrexate in adult patients in the COVID-19 era: an ongoing dilemma. *Lancet Rheumatol.* 2021 Jan;3(1):e9-e10.
  21. Chau CYC, Chow LLW, Sridhar S, Shih KC. Ophthalmological Considerations for COVID-19 Vaccination in Patients with Inflammatory Eye Diseases and Autoimmune Disorders. *Ophthalmol Ther.* 2021 Jun;10(2):201-209.
  22. Ciaffi J, Meliconi R, Ruscitti P, Berardicurti O, Giacomelli R, Ursini F. Rheumatic manifestations of COVID-19: a systematic review and meta-analysis. *BMC Rheumatol.* 2020 Oct 28;4:65.
  23. Ura T, Okuda K, Shimada M. Developments in Viral Vector-Based Vaccines. *Vaccines (Basel).* 2014;29;2:624-41.
  24. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. Updated January 6th 2022 <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html> ( accessed on 1st February 2022)
  25. Predecki M, Clarke C, Edwards H, et al. Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. *Ann Rheum Dis.* 2021 Aug 6:annrheumdis-2021-220626.
  26. Watad A, Quaresma M, Brown S, et al., Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome) - An update. *Lupus,* 2017. 26(7): p. 675-681.
  27. Cunningham ET, Jr. and Moorthy RS, Vaccine-Associated Posterior Uveitis. *Retina,* 2020. 40(4): p. 595-598.
  28. Testi I, Brandão-de-Resende C, Agrawal R, Pavesio C; COVID-19 Vaccination Ocular Inflammatory Events Study Group. Ocular inflammatory events following COVID-19 vaccination: a multinational case series. *J Ophthalmic Inflamm Infect.* 2022;12(1):4. Published 2022 Jan 4.
  29. Rabinovitch T, Ben-Arie-Weintrob Y, Hareuveni-Blum T, et al. Uveitis following the BNT162b2 mRNA vaccination against SARS-CoV-2 infection: a possible association. *Retina.* Aug2, 2021.
  30. Ng XL, Betzler BK, Ng S, et al. The Eye of the Storm: COVID-19 Vaccination and the Eye. *Ophthalmol Ther.* 2022;11(1):81-100.
  31. Bolletta E, Iannetta D, Mastrofilippo V, et al. Uveitis and Other Ocular Complications Following COVID-19 Vaccination. *J Clin Med.* 2021;10(24):5960. Published 2021 Dec 19.
  32. ElSheikh RH, Haseeb A, Eleiwa TK, Elhousseiny AM. Acute uveitis following COVID-19 vaccination. *Ocul Immunol Inflamm.* 2021
  33. Renisi G, Lombardi A, Stanzione M, Invernizzi A, Bandera A, Gori A. Anterior uveitis onset after bnt162b2 vaccination: is this just a coincidence? *Int J Infect Dis.* 2021 Sep;110:95-97.