



New-onset Adult-onset Still's disease-like syndrome after ChAdOx1 nCoV-19 vaccination—a case series with review of literature

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Received: 10 December 2021 / Revised: 11 January 2022 / Accepted: 12 January 2022 / Published online: 18 January 2022
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Abstract

We report a series of 3 Adult-onset Still's disease (AOSD)-like presentations in previously healthy females following vaccination with the ChAdOx1 nCoV-19 vaccine, and also compare them with similar cases reported in literature through a PubMed database search. Our first patient had a high spiking bi-quotidian type of fever with myalgia, sore throat, and arthritis with onset 10-day post-vaccination, with laboratory features of hyper inflammation responding to only naproxen. She was off treatment after 2 months. The second patient, with onset 3-week post-vaccination, had a more severe illness, requiring high dose immunosuppression. In our third case, the onset of illness was slightly delayed i.e., 3-month post-vaccination, but she had the most severe disease with macrophage activation syndrome at presentation requiring immunosuppression and biologicals. The underlying mechanism may be linked to the activation of Toll-like receptors (TLR)—TLR-7 and TLR-9—leading to a robust immune response. These 3 cases highlight the immunogenicity of COVID-19 vaccines, with the possibility of occurrence of new-onset systemic hyper-inflammation illness which can happen a few days following the vaccination, sometimes even delayed to months, and can range in severity from mild to even life-threatening. More cases need to be studied to understand the profile and prognosis of these syndromes in the long run.

Keywords Adult-onset Still's disease · COVID-19 vaccine · Immunology

Introduction

The spread of COVID-19 infection has led to unprecedented rapid growth in vaccine development with a subsequent increase in the vaccination against COVID 19, with many countries having vaccinated more than 50 percent of

their population [1]. India also has completed 1000 million vaccinations since the inception of the vaccination program in Feb 2021 [2]. Fever, chills, myalgia fatigue, and arthralgia can occur following COVID-19 vaccination; however, most of these symptoms are mild to moderate in severity, occurring within the first 3 days of vaccination and resolve within 1 or 2 days [3]. Although deemed safe in the general population, systemic rheumatic diseases have been shown to have flare-ups after vaccination [4]. In addition to this, there are reports of new-onset systemic rheumatological diseases [5, 6]. The adjuvanticity of the available SARS-CoV-2 vaccines is based on either TLR-7/8 or TLR-9 agonism, which is a distinct mechanism from previous vaccines [7]. ChAdOx1 nCoV-19 (Covishield) vaccine, one of the many vaccines available in our country, consists of simian adenovirus vector ChAdOx1, with full-length spike protein of SARS-CoV-2 [8] Here we report a series of 3 cases of new-onset Adult-onset Still's disease (AOSD)-like syndrome following vaccination with ChAdOx1 nCoV-19 vaccine.

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Case 1

A 20-year-old previously healthy female, asymptomatic 4 weeks before admission, presented with high-grade fever (102 degrees Fahrenheit), without chills. The fever was bi-quotidian in nature, with asymptomatic phases in between the fever spikes. This was also associated with throat pain, generalized myalgia, and ankle arthralgia. In a week, she also developed an evanescent maculopapular rash over the neck, abdomen, and thigh during the height of the fever. She had received her first dose of ChAdOx1 nCoV-19 vaccine 10 days before the onset of symptoms. Her clinical examination at the time of admission was unremarkable. On evaluation in an outside hospital, she was found to have neutrophilic leukocytosis (Total WBC count 15,600, N-72%) with elevated C-reactive peptides (71 mg/L) and elevated ferritin levels (3500 ng/ml). The investigations at presentation to us have been summarized in Table 1. Infectious disease (including polymerase chain reaction for SARS-CoV2 and blood culture) and malignancy workup with Positron Emission Tomography–Computerized Tomography (PET-CT)/bone marrow examination were normal. Serological workup for other autoimmune diseases was negative. She was diagnosed with AOSD based on the Fautrel’s criteria [9]. She was initiated on Tab. Naproxen 250 mg twice daily which she had immediate resolution of symptoms of fever and myalgia. She remained afebrile during the remaining stay in

the hospital. She had improvement in her inflammatory parameters at discharge (Table 1). She was continued on anti-inflammatory agents for 4 weeks. She was reviewed telephonically 2 months later and reported to be asymptomatic and has remained off medications since. The course of the patient’s clinical presentation and management has been summarized in Fig. 1.

Case 2

A 47-year-old, previously healthy woman presented with high-grade fever (101 degrees F), quotidian in nature for the last 2 months. This was associated with small and large joint inflammatory arthritis, without any rash. She also had a history of associated significant weight loss and loss of appetite of the same duration. She had a history of ChAdOx1 nCoV-19 vaccine 3 weeks before the onset of symptoms. She had a partial response to oral methylprednisolone therapy 16 mg/day prescribed by a general practitioner. She also gives a positive history of rheumatoid arthritis (RA) in her elder sister. Clinical examination revealed pyrexia with tachycardia (Pulse rate -104 beats per minute) and swollen and painful knee and wrist joints. On evaluation, she was found to have a hemoglobin of 8.1 g/dL, platelet count of 5.54 lakh/mm³, and a white blood cell count of 12,100 cells/mm³ with a neutrophil predominance. She was also found to have elevated liver enzymes and elevated inflammatory markers

Table 1 Baseline investigational parameters of the 3 cases

Parameters	Case 1	Case 2	Case 3	Normal range
Hemoglobin (g/dl)	9.7	8.1	10.6	13.5–17.5
Total leukocyte count (cells/cumm)	10,400 (N-73%)	12,100 (N-82%)	11,700 (N-75%)	4000–12,000
Platelets (lakh cells/cumm)	2.54	5.54	2.24	150,000–450,000
CRP (mg/l)	38	169	227	< 6
ESR (mm/hr)	51	86	48	< 15
SGOT (U/L)	176	29	478	8–40
SGPT (U/L)	262	60	239	5–35
Creatinine (mg/dl)	0.59	0.53	0.8	0.5–1.4
Serum ferritin (ng/mL)	11,491	404	> 100,000	20–300
RF (IU/ml)	< 10.1	< 10.1	Negative	< 20
Anti-CCP (RU/ml)	-	1	Negative	< 10
ANA (done by IF)	Negative	Negative	Negative	Negative
Blood cultures	Negative	Negative	Negative	Negative
Imaging—CT scan/PET-CT	Normal	Normal	Cervical and Inguinal lymphadenopathy	
Echocardiography	Normal	Mild pericardial effusion	Normal	
Bone marrow	Normal	Normal	Consistent with HLH	

RF rheumatoid factor, ANA antinuclear antibody, IIF indirect immunofluorescence, Anti-CCP anti-cyclic citrullinated peptide

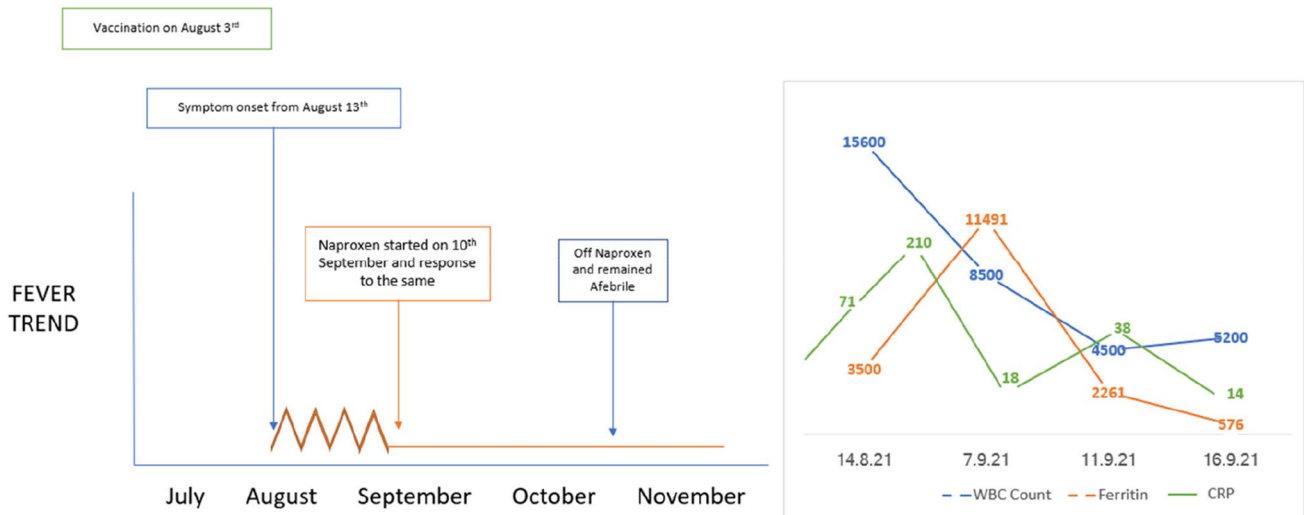


Fig. 1 Clinical course and laboratory values of patient 1 over time

(Table 1). Her nasopharyngeal swab for SARS COV 2 by RT-PCR was negative. Cross-sectional imaging of the thorax and abdomen did not show hepatosplenomegaly and bone marrow examination ruled out the possibility of infection or malignancy. An echocardiogram showed mild pericardial effusion. Serology for autoimmune diseases was negative. After excluding infectious, malignant, and autoimmune etiologies, a possibility of AOSD was considered based on Fautrel’s criteria [9]. Her fever resolved following 20 mg/kg naproxen; however, arthritis needed 0.5 mg/kg oral prednisolone. Since the patient refused consent for higher doses of steroids, she was started on Inj Tocilizumab 162 mg subcutaneously every 2 weeks with low dose methotrexate. She

was reviewed after 1 month telephonically at which point, she had remarkable improvement in her symptoms. A decision regarding further tocilizumab will be done at 3 months review. The course of the patient’s clinical presentation and management has been summarized in Fig. 2.

Case 3

A 35-year-old lady with no previous co-morbidities presented to us with high-grade fever, sore throat, evanescent skin rash on the trunk/extremities, and arthralgias for 2 weeks. There was a history of associated weight loss

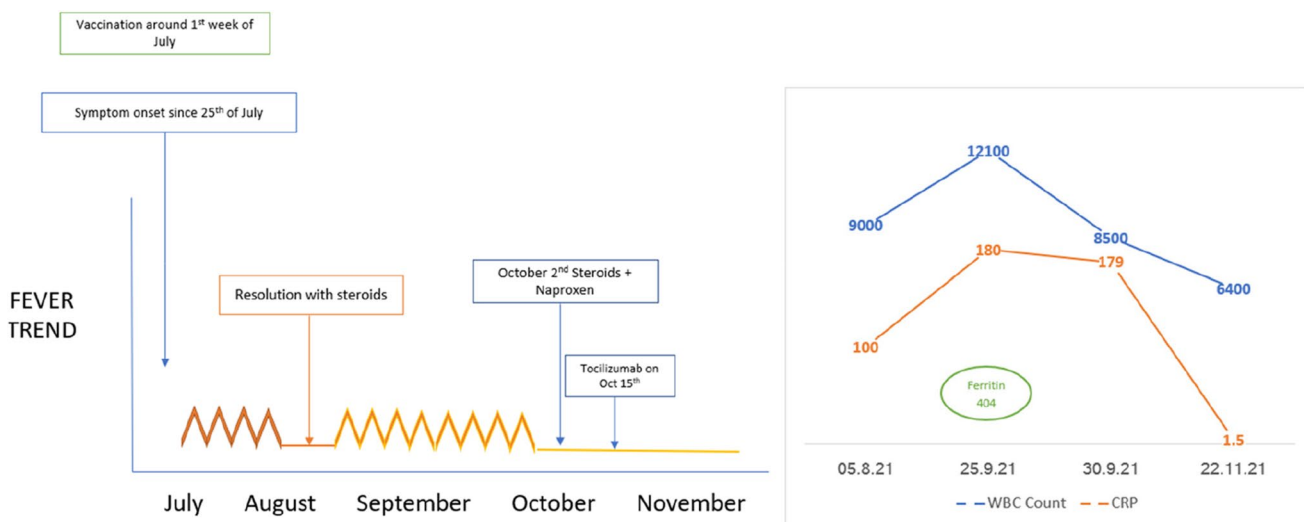


Fig. 2 Clinical course and laboratory values of patient 2 over time

during her morbid period before the presentation. She received her first dose of the ChAdOx1 nCoV-19 vaccine 3 months before the onset of illness. On examination, she was febrile with tachycardia (110/minute). Cutaneous examination showed pink maculopapular rash over the trunk and extremities. Generalized lymphadenopathy was noted. Other systemic examination was unremarkable. Her laboratory tests revealed hemoglobin (Hb) of 10.6 g/dl, white cell counts of 11,700 cells/mm³ with 75% neutrophils, and a platelet count of 2.24 lakhs/mm³. Her C-reactive peptide (CRP) was 227 mg/L. She had elevated liver enzymes (aspartate transaminase of 478 IU/L and alanine transaminase of 239 IU/L) with normal bilirubin levels, elevated lactate dehydrogenase (LDH) (> 1000 U/L), and hyperferritinemia (> 1,00,000 ng/ml). The same has been summarized in Table 1. Fasting serum triglycerides was 336 mg/dL. Her procalcitonin levels were not elevated. Infectious disease workup comprising of 2 sets of blood cultures, nasopharyngeal swab for COVID-19 PCR, echocardiogram, serological tests for Hepatitis A/E/B/C, multiplex polymerase chain reactions (PCR) for Rubella/Epstein Barr virus/Parvovirus B19/Measles/Cytomegalovirus and tropical fever screening were all negative. PET-CT of the whole body showed mild FDG avid bilateral cervical lymphadenopathy in Level I, II, III, and Level V nodes. A cervical node biopsy showed only a reactive lymphadenitis picture with no evidence of granulomas or

lymphoma. Autoimmune disease serologies were negative. During the hospital stay, the fever which was double quotidian in pattern became remittent and she had a drop in blood counts. Bone marrow studies showed no malignancy or infection and confirmed the presence of macrophage activation. A possibility of Adult-onset Still's disease with macrophage activation syndrome was considered. She fulfilled both Fautrel's [9] and Yamaguchi's criteria [10]. She had multi-organ dysfunction in the form of acute respiratory distress syndrome (ARDS) due to diffuse alveolar hemorrhage (DAH) requiring non-invasive ventilation and hepatic failure (AST 515 IU/L, ALT 1294 IU/L, ALP 308 IU/L). She was immediately started on intravenous (IV) pulse methylprednisolone (MP) of 1 g for 3 days with intravenous immunoglobulin (IVIg) 2 g/kg over the next 5 days. We followed up this therapy with oral dexamethasone of 10 mg/m² as per the HLH-2004 protocol [11]. She improved 5 days following this management with rapid clearance of her DAH accompanied by a rise in hemoglobin and blood counts; however, there was no improvement in liver function tests. She further received 480 mg (8 mg/kg) of IV tocilizumab, following which there was a significant improvement in liver function tests. She was discharged on oral prednisolone 1 mg/kg and planned for tocilizumab therapy for the next 3 months. The course of patient management has been summarized in Fig. 3.

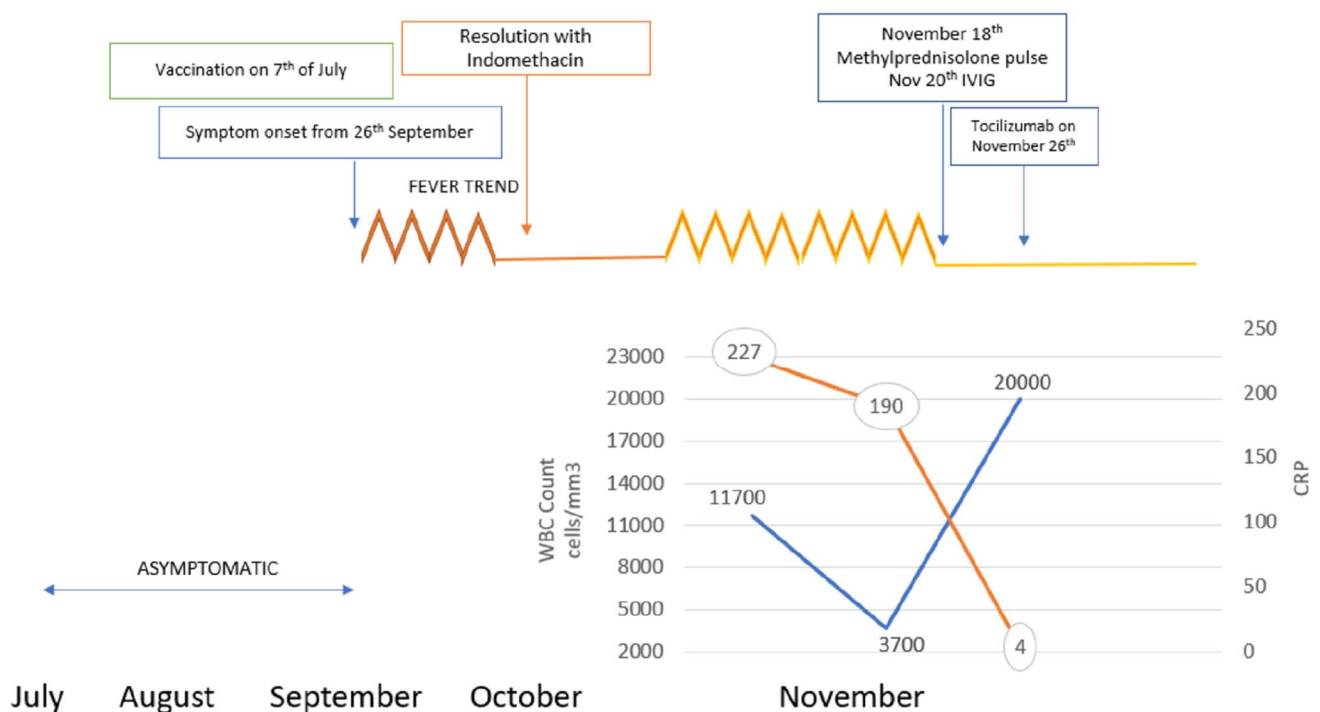


Fig. 3 Clinical course and laboratory values of patient 3 over time

Discussion

AOSD is a multisystem inflammatory disorder of unknown etiology commonly affecting young adults. This is mainly a diagnosis of exclusion, done by a constellation of clinical and laboratory criteria. The cardinal symptoms consist of fever, arthritis, evanescent rash, sore throat, hepatosplenomegaly, and even life-threatening complications, including fulminant hepatitis and macrophage activation syndrome (MAS) [12]. The predominant laboratory abnormalities include anemia, thrombocytosis, neutrophilic leukocytosis, transaminitis, and hyperferritinemia. Abnormal activation of the innate and adaptive immune system leading to uncontrolled production of cytokines, including IL-1 β , IL-6, IL-18, and TNF- α , has been recognized as a cornerstone in AOSD pathogenesis [13]. SARS-CoV-2 infection similarly provokes a hyperinflammatory state driven by IL-6, IL-1 α , IL-1 β , and TNF- α [14]. There have been studies comparing the similarity and differences among AOSD and cytokine storm of COVID-19 [15]. Severe COVID-19 associated cytokine storm is also a hyperferritinemia state which further enhances pro-inflammatory cytokine release [16, 17]. Various autoimmune and rheumatological disorders have been reported among the COVID-19 affected patients and also flare-up of certain underlying rheumatological conditions [6]. Conversely, AOSD is a multisystem auto-inflammatory disorder that can be triggered by viral infections, bacterial infections, or rarely even vaccines in a genetically susceptible individual. Wan-Hee-Yo in his cover letter to the editor also reports a case of AOSD following influenza vaccination [18]. A few differences however do exist between the two disease

states. AOSD has a higher female preponderance which is consistent in our case series. All the 3 cases reported by the authors are female patients [19, 20]. One of the oddities was normal platelet counts in cases 1 and 3. Although thrombocytosis is common in AOSD, it is not a must for diagnosis. There have been many cases reported in the literature where platelet counts are normal [29]. The proportion of elevated liver enzymes and elevated C-reactive peptides was higher in AOSD patients compared to COVID-19 cytokine storm patients. AOSD is characterized by much more elevated ferritin levels compared to the COVID-19 cytokine storm [15]. The cytokines like IL-1, IL-6, and IL-10 were higher in severe COVID-19 compared to AOSD. The common role of IL-1 and IL-6 in the pathogenesis of AOSD and COVID-19 could explain the close similarities between both diseases. cases reported in the literature on the development of AOSD after COVID-19 infection [21, 22]. Apart from the COVID infection, vaccination per se can also cause a new onset AOSD-like syndrome. A PubMed database search done on 2/1/2022 using key words “Still’s disease and COVID vaccination” yielded 3 case reports that have been published in literature [23–25] (Table 2). Two main mechanisms have been postulated in the development of autoimmunity to vaccines: one is molecular mimicry and the other is non-specifically known as “bystander activation” [26]. Studies have shown that the SARS-CoV-2 spike protein can act as a pathogen-associate molecular pattern (PAMP), thereby causing an overproduction of cytokines via the TLR-mediated pathways and also the inflammasome pathway [27, 28]. Activation of TLR-7 and 9 can lead to upregulation of Interferon stimulated Genes (ISG) leading to robust

Table 2 Comparison between various post-COVID vaccine AOSD syndromes reported in the literature

	Case 1	Case 2	Case 3	Magliulo et al. (2021)	Leone et al. (2021)	Baicus et al. (2021)
Age	20/F	47/F	35/F	45/F	36/F	22/M
Type of Vaccine	ChAdOx1 nCoV-19	ChAdOx1 nCoV-19	ChAdOx1 nCoV-19	mRNA-1273	ChAdOx1 nCoV-19	BNT162b2
The onset of symptoms after vaccination	10 days of the first dose	3 weeks of the first dose	3 months of the first dose	5 days of 2 nd dose, 30 days of 1 st dose	4 days of 1 st dose	13 days of the first dose
Duration of symptoms	3 weeks	2 months	1 month	2.5 weeks	3 weeks	1 month
Criteria met	Fautrel’s	Fautrel’s	Yamaguchi	Yamaguchi	Yamaguchi	Fautrel’s
Treatment	Naproxen	Methotrexate, Tocilizumab	MP Pulse IVIg—2 g/kg Tocilizumab (8 mg/kg)	Steroids (1 mg/kg)	MP pulse, anakinra	Mp pulse, IVIG, anakinra
Follow up	2 months	1 month	15 days	3 weeks	1 month	1 month
Response	Improved	Improved	Improved	Improved	Improved	Improved

MP methylprednisolone, IVIG intravenous immunoglobulin

innate immune responses. The symptom onset in all 3 of our cases being later than 1 week following vaccination and symptom constellation lasting > 3 weeks emphasizes the point of these presentations being likely due to a distinct immunological hyperactivation entity, unlike the immediate post-vaccination immunological phenomena. Our first patient had a less severe disease that responded to only naproxen; however, the second patient had a more severe disease. The third patient had a life-threatening presentation requiring intravenous immunoglobulin, pulse steroids, and anti-cytokine therapy to control the disease activity. The time difference between the COVID vaccination and AOSD-like presentation was relatively short (days to weeks) in the first two cases; however, it was slightly delayed (3 months) in Case 3. The delayed onset as in Case 3 is also in contrast to the recently reported cases of AOSD-like state following COVID vaccination, which had onset ranging from 5- to 13-day post-vaccination [22–24]. Such observations highlight the point that hyperinflammatory state following COVID19 vaccination can be variable in severity from mild to life-threatening disease and can present early (in days/few weeks) or occur as a delayed presentation (up to 3 months).

At this point, the nomenclature of the abovementioned presentations seems difficult and could be debatable. Such presentations could turn out to be a monophasic illness in contrast to the variable course of AOSD. However, similar cases from across the globe need to be reported and long-term follow-up of our patients is imperative to conclude on this aspect. With this case series, we can only postulate the COVID vaccination to be the most probable inciting trigger for an AOSD like presentation; however, a definite causal relationship can only be established with the help of epidemiological studies from countries with good data-keeping and surveillance for vaccine-induced immunological adverse events and population data of annual incidence of AOSD.

Conclusion

Clinicians must be alert to the possible occurrence of new-onset early or delayed presentation of an AOSD-like syndrome following ChAdOx1 nCoV-19 vaccination. The presentation can range from being mild to extremely life-threatening. Timely identification and institution of appropriate anti-inflammatory therapy based on the severity of presentation would be imperative.

Acknowledgements We would like to thank Dr. Prabhu Vasanth for his contributions to the manuscript.

Author contribution SP: original hypothesis, conceptualisation, literature review, writing—original draft, review, and editing; NK:

conceptualisation, literature review, writing—original draft, review, and editing; JM: writing—original draft, review, and editing; CAS: conceptualisation, writing original draft—review and editing; DD: conceptualisation, review, and editing; BAS: conceptualisation, review, and editing; ST: conceptualisation, review, and editing; AG: original hypothesis, data review, data interpretation, manuscript preparation; writing—review and editing.

Data availability Data would be made available on request.

Declarations

Informed consent Written informed consent has been obtained from all the patients before preparing this manuscript.

Conflict of interest AG reports receiving an honorarium for an invited guest lecture from Chugai Pharmaceuticals, Japan, outside the scope of this study. SP, NK, JM CAS, DD, BAS, and ST have no conflict of interest to declare.

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