Impact of COVID-19 pandemic on uveitis patients receiving immunomodulatory and biological therapies (COPE STUDY)

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► Supplemental material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bjophthalmol-2020-317417).

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Received 5 July 2020
Revised 29 August 2020
Accepted 23 September 2020

To cite: Agarwal AK, Sudharshan S, Mahendradas P, *et al. Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year].doi:10.1136/bjophthalmol-2020-317417

ABSTRACT

Purpose To evaluate the change in the ongoing immunomodulatory (IMT) and biological therapies among patients with non-infectious uveitis (NIU), and determine the number of uveitis relapses during the COVID-19 pandemic.

Methods In this national multicentric prospective case series, data of subjects with NIU receiving corticosteroids, systemic IMT and/or biological agents were analysed. The data collection was performed from 1 March 2020 to 25 June 2020. Main outcome measures included change in the ongoing treatments with corticosteroids, IMT and biological agents, use of alternate therapies and rates of uveitis relapse.

Results In this study, 176 patients (284 eyes) with NIU (mean age: 33±17.1 years; males: 68) were included. A total of 121 eyes (90 patients) were deemed to have active NIU. Of these, seven subjects (7.8%) did not receive intravenous methylprednisolone despite need felt by the treating uveitis experts. In addition, 35 subjects (57.4%) received a rapid tapering dosage of oral corticosteroids despite active disease. A total of 161 (91.5%) subjects were receiving systemic IMT and 25 (14.2%) were on biological therapies. Overall, IMT was altered in 29/161 (18.0%) subjects. Twenty-two eyes were treated with intravitreal therapies in the study period. Fifty-three eyes (32.5%, 29 subjects) developed relapse of NIU, of which 25 subjects (86.2%) were deemed to have reactivation related to altered systemic IMT. No patient developed COVID-19 during follow-up.

Conclusions During the ongoing COVID-19 pandemic, uveitis specialists may tend to reduce the ongoing systemic IMT, or prefer less aggressive treatment strategies for NIU. These subjects may be at high risk of relapse of uveitis.

INTRODUCTION

A novel coronavirus, designated as COVID-19 (coronavirus disease of 2019), emerged in Wuhan, China, at the end of 2019. This novel coronavirus is a single-stranded RNA virus which is highly transmissible and has a high fatality rate. It has been observed that high fatality is associated with risk factors for severe COVID-19 infection. These risk factors include age above 50 years (in some countries, the limit is placed at 60–65 years), presence of comorbidities such as cardiovascular disease, respiratory system disease, systemic arterial hypertension, diabetes mellitus, obesity (body mass index >40), and active systemic inflammatory disease.[1–5] These patients may develop a more vigorous immune response inducing a cytokine storm. Henry *et al*[6] have performed a meta-analysis studying various haematological, biochemical and immune biomarker abnormalities that are associated with severe COVID-19 disease and high mortality. The authors observed that systemic inflammatory cytokines such as interleukins 6 (IL-6) and 10 (IL-10), apart from serum ferritin were strong discriminators for severe disease.

Uveitis is an important manifestation of several systemic inflammatory conditions. Thus, patients of uveitis may be considered to be at high risk of severe COVID-19 disease. During the early stages of COVID-19 pandemic, that is, March 2020, there was considerable anxiety worldwide among uveitis specialists regarding the use of high-dose corticosteroids and immunomodulatory therapies (IMT) in their patients. Several patients with uveitis are on high-dose corticosteroids (≥1 mg/kg/day oral prednisolone or equivalent), IMT and/or biological agents, raising fears of increased susceptibility to COVID-19 infection and severe forms of the disease.[7–9] Anticipating a change in the practice patterns, major uveitis societies have published evolving guidelines on the use of IMT and biological agents.[10] Organisations such as International Uveitis Study Group (IUSG), International Ocular Inflammation Society (IOIS) and Foster Ocular Immunology Society (FOIS) have issued ongoing recommendations beginning in March 2020, based on a consensus among experts.[10]

More recently, there has been a focused effort by various international expert organisations and specialists to determine the role of IMT on COVID-19 infections in uveitic diseases, and to alleviate the anxieties of practicing uveitis specialists.[10 11] The current perspective among physicians for autoimmune and rheumatological conditions is that corticosteroids should be used at the least possible dose, and systemic IMT (especially those agents that do not affect antiviral immunity) may be continued in the absence of COVID-19 infection.[12 13] However, there is no real-world data on the course of subjects with uveitis during this ongoing COVID-19 pandemic, especially from countries with a large population burden of both uveitis and COVID-19 infections, such as India. Here, we report

a national multicenter prospective case series of patients from India with non-infectious uveitis (NIU) on treatment with corticosteroid and/or IMT/biological agents to assess the impact of the COVID-19 pandemic on uveitis management.

MATERIALS AND METHODS

This study was a national prospective case series performed in major tertiary eye-care centres in India (listed in online supple mental table 1). The study was conducted as per the Tenets of Declaration of Helsinki, and Institute Ethics clearance was obtained from all the study centres for the conduct of the study. Written informed consent was obtained from all the study participants. Established patients with a diagnosis of non-infectious anterior, intermediate, posterior or panuveitis who were receiving IMT and/or biological therapies in the pre-COVID period and assessed for follow-up between 1 March and 25 June 2020 (approximately 4 months) were included.

For every participating centre, eligible cases were reported to one responsible coordinating researcher at PGIMER, Chandigarh (AKA.). The data collection was performed based on ophthalmic examination in the Department of Ophthalmology at various participating centres. From all the included subjects, clinical details including previous ocular disease, medical history, laboratory features, previous corticosteroid, IMT and biological therapies were noted. The data collection for ocular signs and symptoms was performed by in-person examination. The demographic and clinical details of the subjects were noted. The details of examination, including slit-lamp evaluation of anterior segment cells and flare, iris nodules, vitritis, active choroiditis/retinitis, retinal vasculitis and other features were noted. Serial evaluation of the subjects was performed to determine if there was a relapse of uveitis. The frequency of evaluation ranged from daily to 4 weeks based on the type and severity of the uveitis. If any subject developed COVID-19 while on treatment, it was noted as well.

The details of change in treatments (drug, dose or regimen) during this period, and the disease activity including quiescence, time since last 'activity', and relapse of uveitis was noted. Use of oral/intravenous corticosteroids, and the alterations in ongoing systemic IMT/biological therapies was noted. Rapid taper of oral corticosteroids was defined when the subjects received a taper >10 mg/week oral prednisolone. If the uveitis experts used alternate therapies instead of aggressive therapeutic strategies (such as intravenous pulse corticosteroids or systemic IMTs), the details of the same were recorded. The data were collected on an online secure platform specially designed for the COVID-19 pandemic based on the Collaborative Ocular Tuberculosis Study (COTS) group.[14] All the data were collected as variables defined in the online platform. The collected data were screened and populated as mean, SD, and percentages. Inter-group comparison for determining differences in time since last uveitis activity was performed using Mann–Whitney U-test. Statistical analysis was performed using GraphPad Prism 8 (GraphPad Software, San Diego, California, USA). A p value of <0.05 was considered as statistically significant.

RESULTS

One hundred and seventy-six patients (284 eyes) with NIU (mean age: 33±17.1 years; males: 68) visiting major tertiary-care eye hospitals were included in the study. The demographic and clinical data of the subjects are provided in table 1. One hundred and eight (61.4%) patients had bilateral disease. At the time of enrolment, 121 eyes (90 patients) were deemed to have active NIU, whereas the remaining patients were quiescent on maintenance therapy. Among 163 eyes with inactive NIU at baseline, the mean time since last activity was 22.3±15.6 weeks.

Among eyes with active NIU, 11 patients were treated with intravenous methylprednisolone (IVMP) for severe vision-threatening uveitis. However, in seven subjects, the uveitis experts preferred to not treat with IVMP despite an indication for the same. Among the subjects with active NIU who were initiated on oral corticosteroids during the study, the uveitis experts preferred to rapidly taper the medication (>10 mg/week) in 35 subjects (57.4%). However, no alterations were made in the oral corticosteroid regimen for subjects who were

Table 1 Baseline demographic and clinical characteristics of patients with uveitis analysed during the COVID-19 pandemic

Parameter	All patients (n=176; 284 eyes)
Mean age, years±SD	33±17.1
Number of males, n (%)	68 (38.6)
Number of patients with bilateral disease, n (%)	108 (61.4)
Anatomical location of uveitis	
Anterior, n (%)	45 (25.6)
Intermediate, n (%)	20 (11.4)
Posterior, n (%)	54 (31.2)
Panuveitis, n (%)	57 (32.4)
Aetiological diagnosis	
Undifferentiated uveitis, n (%)	64 (36.4)
Retinal vasculitis, n (%)	23 (13.5)
Sarcoidosis, n (%)	15 (8.5)
HLA B27-related uveitis, n (%)	13 (7.4)
Vogt-Koyanagi-Harada's disease, n (%)	12 (6.8)
Behcet's uveitis, n (%)	10 (5.7)
Serpiginous choroiditis, n (%)	10 (5.7)
Others, n (%)	29 (16.5)
Number of eyes with active uveitis (number of patients)	**121 (90)**
Ongoing medications	
Topical corticosteroids (number of eyes), n (%)	73 (25.7)
Topical cycloplegic agents (number of eyes), n (%)	56 (19.7)
Topical NSAIDS (number of eyes), n (%)	44 (15.5)
Oral corticosteroids (number of subjects), n (%)	94 (53.4)
Intravenous corticosteroids (number of subjects), n (%)	11 (6.2)
Oral azathioprine (number of subjects), n (%)	61 (34.7)
Oral mycophenolate mofetil (number of subjects), n (%)	24 (13.6)
Oral/subcutaneous methotrexate (number of subjects), n (%)	71 (40.3)
Oral tacrolimus (number of subjects), n (%)	2 (1.1)
Oral ciclosporin (number of subjects), n (%)	1 (0.6)
Oral cyclophosphamide (number of subjects), n (%)	1 (0.6)
Subcutaneous adalimumab (number of subjects), n (%)	16 (9.1)
Intravenous tocilizumab (number of subjects), n (%)	3 (1.7)
Intravenous rituximab (number of subjects), n (%)	2 (1.1)
Prevalence of complications of uveitis	
Band-shaped keratopathy (n, %)	5 (1.8)
Secondary cataract (n, %)	49 (17.2)
Macular oedema (n, %)	41 (14.4)
Optic nerve oedema (n, %)	20 (7.0)
Epiretinal membrane (n, %)	19 (6.7)
Ocular hypertension/glaucoma (n, %)	17 (6.0)

on maintenance therapy (≤10 mg/kg/day dose). The details of the systemic corticosteroid therapy and its alteration during the pandemic are provided in table 2.

In the cohort, 161 (91.5%) patients were receiving systemic IMT, and 25 patients (14.2%) were receiving biological therapies at baseline. Overall, the treating uveitis specialists altered IMT in 29/161 (18.0%) subjects, but no alterations were made in the treatment with biological agents. The details of the systemic IMT and biological therapies are provided in table 3. Details of topical and intravitreal therapies employed during the study period are listed in tables 4 and 5, respectively. During the pandemic, 22 eyes were treated with intravitreal injections (single injection each). The indications for which intravitreal therapies were administered are provided in table 5.

Among eyes with inactive NIU (n=163 eyes), relapse of the disease was noted in 53 eyes (32.5%, 29 subjects) during the study period (online supplemental table 2). Thus, 24 subjects had relapse in both eyes. In our series, nine subjects stopped medications on their own, of which five subjects developed active uveitis. The relapse was deemed to be related to altered therapies in 25 subjects (86.2%). In these eyes, the mean time since last uveitis activity was 16.3 ±9.3 weeks, which was significantly shorter than in eyes without relapses (25.2±17.1 weeks) (p=0.001). All these subjects were treated with a bridge course of oral corticosteroids and frequent topical corticosteroids/intravitreal injections. None of the subjects were started on additional systemic IMT during this period by treating uveitis specialists. None of the subjects developed symptoms related to COVID-19 during the study period.

DISCUSSION

It is imperative to understand the treatment patterns and the outcomes of ocular inflammation during this COVID-19 pandemic. When this study was initiated in March 2020, the guidelines for the use of corticosteroids and IMT in subjects with uveitis were either not available or were preliminary and still evolving. Thus, none of the centres included in our study followed any particular protocol for reducing systemic corticosteroids and IMT in their patients. Currently, there is little evidence to guide the course of COVID-19 infection in subjects on IMT. Certain authors have suggested increased risk of severe COVID-19 disease in subjects on systemic IMT, especially those

Table 2 Therapies with systemic (oral and intravenous) corticosteroids and their alteration due to the COVID-19 pandemic

Intravenous corticosteroids	
Number of patients who received intravenous corticosteroids	11
Number of patients who required but did not receive intravenous corticosteroids*	7
Oral corticosteroids	
Total number of patients on oral corticosteroids during the study period (out of 176 patients)	94 (53.4%)
Number of patients on oral corticosteroids in maintenance phase†	33 (35.1%)
Number of patients initiated on oral corticosteroids for active uveitis‡	61 (64.9%)
Number of patients who were initiated on oral corticosteroids for active uveitis, and received rapid tapering regimen (>10 mg/week reduction in dose)	35 (57.4%)
Number of patients who required oral corticosteroids for active uveitis but did not receive§	20 (22.2%)
Number of patients who stopped corticosteroids on their own	8

*Indicates patients who required intravenous corticosteroids for severe uveitis as deemed by the treating ophthalmologist.
†Indicates those patients who were already on a stable dose of ≤10 mg/kg/day oral prednisolone at the beginning of the study since their uveitis was deemed to be quiescent/inactive.
‡Indicates the number of patients who were initiated on high-dose oral corticosteroids for active uveitis (1 mg/kg/day oral prednisolone).
§Indicates patients who required oral corticosteroids for active uveitis as deemed by the treating ophthalmologist, but were treated with other agents such as intravitreal therapies.

Table 3 Therapies with systemic immunosuppressive and biological agents and their alteration due to the COVID-19 pandemic

Total number of patients on systemic immunosuppression			**161 (91.5%)**	
Total number of patients on biological therapies			**25 (14.2%)**	
Agent	**Number of patients receiving treatment (ongoing) (n=176)**	**Number of patients in whom treatment was altered (mean reduction in dosage/day±SD)***	**Number of patients developing relapse†**	**Mean time to develop relapse (weeks ±SD)**
Azathioprine	61	12 (50±21.3 mg)	12	5.8±1.7
Methotrexate (oral)	34	10 (5.2±3.4 mg)	4	7.2±2.2
Methotrexate (subcutaneous)	37	4 (8.7±4.8 mg)‡	4	9±3.4
Mycophenolate mofetil	24	3 (666.7±288.7 mg)	3	8.7±3.1
Tacrolimus	2	–	0	–
Cyclosporine	1	–	0	–
Cyclophosphamide	1	–	0	–
Adalimumab	16	–	0	–
Tocilizumab	3	–	0	–
Rituximab	2	–	0	–

*Indicates the number of patients in whom the treatment with immunosuppressive/biological agents was altered during the course of the study.
†Indicates the number of patients with a relapse due to alteration in the dose of the corresponding immunosuppressive/biological agent.
‡In one subject, treatment with subcutaneous methotrexate which was ongoing at a dose of 15 mg/week was stopped by the patient.

Table 4 The use of topical medications and their alterations in patients with uveitis during the COVID-19 pandemic

Agent	Number of eyes receiving treatment (ongoing) (n=284)	Number of eyes in whom frequency of drops was altered (increased*, initiated†)
Betamethasone 1%	31	20*, 9†
Dexamethasone 0.1%	20	8*, 3†
Prednisolone acetate 1%	22	8* 3†
Flurbiprofen 0.3%	19	4*
Ketorolac 0.5%	5	3*
Nepafenac 0.1%	20	–
Atropine 1%	42	12*
Homatropine 2%	34	4* 3†

*Indicates the patients in whom the frequency of topical medications were increased from existing therapy.
†Indicates the patients in whom new treatments were started.

Table 5 The use of intravitreal/periocular therapies in patients with uveitis during the COVID-19 pandemic

Number of eyes receiving local therapies				**22**
Number of eyes receiving local therapies due to disease reactivation related to reduced systemic therapy				**7**
Agent	**Number of eyes receiving treatment***	**Indications**	**Number of eyes receiving treatment**	**Number of eyes with relapse due to changed systemic therapy†**
Dex implant	10	Active choroiditis	1	1
		VKH disease	2	2
		Macular oedema	4	0
		Retinal vasculitis	2	2
		Intermediate uveitis	1	1
Triamcinolone (periocular)	6	Macular oedema and active vasculitis	6	0
Triamcinolone (intravitreal)	2	Active vasculitis	2	1
Ranibizumab	4	Macular oedema	4	–

*Each eye received a single injection of the pharmacological agent.
†Indicates the number of eyes that received intravitreal/periocular therapies due to disease reactivation which was related to reduction in doses of systemic corticosteroids or immunomodulatory therapy.
Dex, Dexamethasone; VKH, Vogt-Koyanagi-Harada's disease.

on heart/kidney transplant and other multiorgan morbidities. Based on these reports, it is likely that the treating uveitis specialists preferred to reduce dosages of systemic IMT in their patients included in our study. However, thereafter, evolving literature suggests that there is no evidence of aggravated course of COVID-19 disease in patients on chronic IMT.[12 13]

There is still an ongoing dilemma in the use of high-dose oral corticosteroids during the COVID-19 pandemic, with fears of increased susceptibility to severe respiratory infection.[10 11] On the other hand, during later course of the disease when the patients require oxygen support or mechanical ventilation, corticosteroids may have a protective role against the inflammatory response though large trials have shown variable results in the mortality rates.[15 16] The treating physicians and patients may be anxious in initiating high-dose oral corticosteroids for ocular indications in otherwise non-COVID infected healthy subjects. In addition, in our series, several subjects themselves stopped oral corticosteroids on their own due to the fear of increased susceptibility to coronavirus infection, and thus developed a relapse of uveitis. Therefore, this analysis is pertinent in the present times to highlight the consequences of abrupt corticosteroid dose reduction.

We observed that nearly 32% eyes (29 subjects) in our cohort developed relapse of NIU, of which 86.2% (25 subjects) developed active uveitis due to altered systemic therapies. These patients had either received reduction in the dosages of their ongoing systemic IMT by the treating uveitis specialists, or had stopped medicines (including oral corticosteroids and IMT) on their own (online supplemental table 2). We observed that some uveitis experts preferred to use either oral corticosteroids, or other local therapies when they felt that intravenous corticosteroids were indicated (table 2). Further, uveitis experts preferred a rapid taper of oral corticosteroid therapy in 35 out of 61 subjects with active NIU at baseline despite active inflammation (table 2). It is noteworthy that subjects who abruptly stopped oral corticosteroids/IMT on their own, or received a reduced dosage of IMT, developed relapses, whereas those who received oral corticosteroids/local therapies instead of intravenous corticosteroids, or a rapid taper of oral corticosteroids (under the supervision of the treating uveitis specialist) did not show any relapse. Thus, our data show that abrupt withdrawal of corticosteroids and untimely reduction of IMT can place the patient at a high risk of relapse. On the other hand, use of appropriate alternate therapies, and low doses of oral corticosteroids after a rapid taper may not be associated with such a risk.

The subjects who developed active disease during the study period were treated with a bridge course of oral corticosteroids, with or without concomitant increase in ongoing systemic IMT, and local intravitreal/periocular therapies. The uveitis experts also preferred the use of local periocular or intravitreal therapies in certain situations when the disease had recurred (these subjects had not received local therapies previously) (table 5 and online supplemental table 1). None of the subjects who received local therapies showed active disease during the study period.

In our series, we observed that the subjects who relapsed had a significantly less time since last uveitis activity detection (16.3 weeks vs 25.2 weeks; p=0.001). Thus, subjects in whom uveitis has been previously under long-term remission may be at a lower risk of a relapse. This is in line with literature on acute anterior uveitis by the Systemic Immunosuppressive Therapy for Eye disease (SITE) cohort study group which demonstrated that the risk of first relapse of uveitis may diminish among subjects still free of relapse after 2 years.[17] However, in subjects who have had a recent control of their inflammation, alterations in therapies may put them at a higher risk of disease reactivation. In these patients, relapse can be treated with either a bridge course of oral corticosteroids or local therapies, or a combination of both. Apart from the use of corticosteroids, it is imperative to continue ongoing systemic IMT to prevent the risk of future reactivation. These subjects require a close follow-up and careful titration of their systemic therapies to avoid serious visual morbidity.

Relapse of uveitis can pose a serious challenge to the visual function of subjects with NIU, and can result in permanent damage to the uveal tissue. Subjects with ongoing therapies for NIU such as IMT and biological agents require frequent monitoring and adherence to therapy to maintain long-term quiescence. The goal of treatment in these patients is to reduce the number of recurrences and maintain quiescence. The adverse events with long-term systemic corticosteroids have promoted gradual inclination towards non-corticosteroid therapy for the management of NIU. Off-label systemic IMT is often prescribed to the patients who do not adequately respond to corticosteroids.[18] A number of large, multicenter efforts have elaborated the safety and use of systemic IMT and biological agents for NIU. The Fundamentals of Care for Uveitis (FOCUS) initiative, an international expert collaboration has recommended the use for non-steroidal therapy for the management of NIU.[19] Therefore, our study shows that in subjects with stable ongoing therapies for NIU, sudden reduction in dosages due to the COVID-19 situation can result in undesirable significant number of uveitis recurrences. These patients can require aggressive bridge therapy with oral or intravenous corticosteroids, which in addition to the risk of complications may require closer follow-up, further burdening the healthcare system.

Our study has a number of limitations. Since this is an observational study, and no interventions are being performed, the study is not aimed to be a clinical trial, and cannot determine the therapeutic value or clinical utility of certain anti-inflammatory therapies. In addition, the study cannot make any recommendations on the screening, diagnosis, treatment or follow-up of patients with uveitis and COVID-19, for which a multi-pronged and multidisciplinary prospective study will be required. The study enrolment begun at the time when the total number of COVID-19 patients was low in India. The rate of new cases per million population was 0.001 per million in March 2020, which increased to 12.2 per million by the end of June 2020.[20] As in any multicenter study, there may be shortcomings in the data collection/entry leading to errors in the analysis. However, the authors have used the system of online data collection in a smart form-based website previously in analysing a large study data set from the COTS.

In summary, this study presents novel data on the course of subjects with NIU during the COVID-19 pandemic. Our data reveals that patients with ocular inflammation are at high risk of disease relapse due to precipitous alterations in IMT and biological therapies. Therefore, it is important for the uveitis specialists to be aware of the consequences of reduction in systemic IMT and other therapies. The results of the COPE study along with the data from rheumatology and transplant literature can help agencies, and professional societies make adapted recommendations for patients with uveitis during the COVID-19 pandemic.

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Contributors Conceptualisation and study design: AKA, VG, RA; study data, and data analysis and interpretation.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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