• Clinical Research •

First contact investigations and compliance to treatment in patients with uveitis

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Abstract

• **AIM:** To ascertain the pattern of investigations at first contact in uveitic patients and evaluate compliance to treatment.

• **METHODS:** An observational study comprised of 201 uveitic patients presenting for the first time to our centre from January 2019 to June 2020. Detailed information regarding systemic investigations undertaken by specialists at the time of first contact and the cost of these investigations were reviewed on the first visit to our centre. Compliance with the treatment was determined and reasons behind non-compliance were evaluated on the first follow-up in patients who had no improvement in clinical signs and symptoms.

• **RESULTS:** The mean age of the study group was 35.35±14.1y and gender composition was 59.7% males and 40.3% females. Anterior uveitis was observed in 45.3% of patients, intermediate uveitis in 31.8% of patients, posterior uveitis in 14.9% of patients and panuveitis in 8.0% of patients. Association with a systemic disease was evident in 17.9% of patients. When compared with standard guidelines and uveitis patterns, systemic investigations were identified to be relevant only in 38.3% of patients. Non-compliance to treatment was documented in 22.4% of patients. Common reasons for non-compliance were inadequate counselling by the treating physician about treatment in 26.7% of patients and a busy schedule at work/school in 22.2% of patients.

• **CONCLUSION:** Significant number of investigations performed at first contact is found to be contrary to standard guidelines and are not contributory to the care. About a quarter of patients in this study are found to be non-compliant with the treatment. Compliance is more challenging to achieve in school-going children and working adults. The availability of comprehensive, periodically updated, evidence-based guidelines on the role of investigations and the use of trained counsellors may help to channelize proper evaluation and improve compliance to treatment, respectively, in patients with uveitis.

• **KEYWORDS:** uveitis; compliance; investigations; first contact

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INTRODUCTION

Uveitis is defined as inflammation of uveal tissue either in its entirety or of its component structures, the iris, ciliary body, and choroid. It may be associated with inflammation of adjacent ocular tissues like the retina, sclera, cornea, vitreous and optic nerve. In North America, the annual incidence of uveitis ranges from 17 to 52 per 100 000 persons and prevalence ranges from 58 to 115 per 100 000 persons[1]. Uveitis is considered to be responsible for 10% of worldwide blindness[2]. Uveitis can be associated with some systemic disease; therefore, a systematic approach to a patient with uveitis is essential to identify these associated or causative conditions[3-5]. Hence, there is a need for eliciting a detailed history and performing a meticulous clinical evaluation, of both the eyes as well as other organs of the body. A tailored approach to laboratory investigations based on meticulous history and comprehensive ocular evaluation has been considered the gold standard for the successful management of uveitis[6]. The choice of investigations should be based on clinical clues, available standard guidelines, and strength of evidence so as to prevent additional financial burden to the patient as well as reduce the risks associated with obtaining a false positive result. However, with advancements in

technology and shifting emphasis on revenue generation, a tailored approach may no longer be a widely practised option in managing patients with uveitis. This practice is further compounded by the lack of laboratory regulations in most countries.

In addition, as uveitis care often requires prolonged treatment and long-term follow-up, adherence to treatment is of paramount importance. It is well-recognized that poor initial management of uveitis will lead to the condition becoming chronic and increasingly resistant to standard treatment. This leads to poor visual outcome and long-term morbidity.

However, there is a paucity of literature regarding the pattern of investigations being performed during the management of uveitis in middle-low economic countries wherein laboratory regulations are generally lacking. In addition, there is a broader lack of published data on the compliance of patients with uveitis treatment.

In this study, we describe our observations regarding the pattern of investigations that were advised at the first contact with a specialist. We also present our data on the proportion of patients who were not compliant with the recommended treatment and the reasons thereof.

SUBJECTS AND METHODS

Ethical Approval This was a single-centre, institutional, descriptive observational study conducted at a tertiary eye care centre in North India between January 2018 to June 2020. Institutional Ethics Committee approval was obtained before the initiation of the study (approval number: IECPG-533/14.11.2018). Patients with previously diagnosed uveitis presenting to our outpatient department and uvea clinic for the first time were enrolled into the study after obtaining informed consent. Patients with secondary complications like elevated intraocular pressure and cataract were excluded from the study.

Details like age, gender, history regarding the ocular disease and any associated systemic illness, past treatment history and ocular surgery were noted on the case records. All the cases were anatomically classified into anterior, intermediate, posterior uveitis and panuveitis. Study-specific documentation included enlisting all the available records of investigations that had already been undertaken before presentation to our centre and determining an approximate amount of money spent on these investigations, by the patient. Patients who did not bring their complete record of investigations were asked to bring them on the next follow-up. A detailed ocular examination was conducted for all patients. Patients were specifically asked regarding compliance-related issues if we noticed less than expected response during the first follow-up visit and in those who developed early recurrence.

Few operational definitions were used to maintain the clarity of our aim and objectives. Relevant investigation included investigations recommended by standard, internationally recognized textbook(s) on uveitis taking into consideration the anatomical category of uveitis[7]. Thus, investigations in a patient would be considered relevant only if it is based on the presence of other suggestive history, symptoms and/or signs or to ascertain the risk of reactivation of an endemic disease (*e.g.*, tuberculosis, hepatitis). Tests carried out without these reasons would be categorized as non-relevant, as studies have shown that there is poor diagnostic and management utility, without a tailored approach.

Treatment compliance indicated adherence to treatment recommended by the physician, taking into cognizance, standard instructions to be provided by the physician at the time of starting therapy. Treatment non-compliance comprised of patients who stopped treatment on their own, self-medicated themselves, used drops in the wrong eye, used less frequency of medications, wrong or no tapering of steroids, did not initiate treatment or not take prescribed medications, and did not shake the eyedrops (when a suspension was prescribed) before use.

Data was recorded in Microsoft Excel Spreadsheet 2016 and analysis was undertaken using STATA/SE 12.1 version software.

RESULTS

Two hundred and one patients were recruited for the study. The mean age was 35.35±14.1y, with 120 male (59.7%) and 81 female (40.3%) patients. Anterior uveitis was diagnosed in 91 (45.3%) patients, intermediate uveitis in 64 (31.8%), posterior uveitis in 30 (14.9%), and panuveitis in 16 (8.0%) patients. The 21.9% of cases had acute uveitis, 44.8% had chronic uveitis, and 33.3% had recurrent uveitis at the time of presentation.

The 20.9% of cases had associated systemic complaints, joint pain being the most common (12.4%). History of oral ulcers and exertional dyspnoea was elicited in 2% and 3% of patients respectively. Systemic associations were identified in 17.9% of patients (Table 1).

The most common systemic history was that of tuberculosis (8.5%). Among 201 uveitis patients, 19 patients were on anti-tubercular therapy (ATT) at the time of presentation to our centre. Two patients were started on ATT based on presumed ocular tuberculosis and 17 were started/had been treated earlier, for diagnosed systemic tuberculosis. At presentation, 17 patients were on ATT for systemic tuberculosis, of which 13 were for pulmonary tuberculosis, 2 patients for brain TB, 1 patient for skin TB, and 1 patient for bone TB. Out of 19 tuberculosis patients, 26.3% of tuberculosis patients on ATT were registered at the directly observed therapy, short-course (DOTS) centre. Two patients on ATT developed side effects due to ATT drugs. One patient had developed hepatotoxicity and one patient had optic neuritis.

Table 1 Systemic etiology of uveitis *n* (%)

Systemic diagnosis	Anterior uveitis (*n*=91)	Intermediate uveitis (*n*=64)	Posterior uveitis (*n*=30)	Panuveitis (*n*=16)	Total
Sarcoidosis	2 (2.2)	3 (4.7)	0	2 (12.5)	7 (3.5)
Systemic TB	7 (7.7)	7 (10.9)	3 (18.7)	0	17 (8.5)
Behcets disease	0	1 (1.5)	1 (3.3)	1 (6.2)	3 (1.5)
Hepatitis B	0	1 (1.5)	0	1 (6.2)	2 (1.0)
Rheumatoid arthritis	0	0	1 (3.3)	0	1 (0.5)
Ankylosing spondylitis	3 (3.3)	2 (3.1)	0	0	5 (2.5)
Wegener's granulomatosis	1 (1.1)	0	0	0	1 (0.5)
Total	13 (14.3)	14 (21.9)	5 (16.7)	4 (25.0)	36 (17.9)

TB: Tuberculosis.

Table 2 Investigations undertaken before presentation *n* (%)

Parameters	Anterior uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis	Total
Chest X-ray	75 (45.5)	52 (31.5)	25 (15.2)	13 (7.9)	165 (82.1)
Complete blood count	78 (43.1)	57 (31.5)	30 (16.6)	16 (8.8)	181 (90.1)
Mantoux test	70 (44.9)	46 (29.5)	27 (17.3)	13 (8.3)	156 (77.6)
ESR	64 (43.2)	49 (33.1)	22 (14.9)	13 (8.8)	148 (73.6)
VDRL	15 (39.5)	14 (36.8)	7 (18.4)	2 (5.3)	38 (18.9)
ACE	19 (35.9)	23 (43.4)	6 (11.3)	5 (9.4)	53 (26.4)
ANA	7 (35)	8 (40)	4 (20)	1 (5)	20 (10)
ANCA	5 (45.5)	3 (27.3)	2 (18.2)	1 (9.1)	11 (5.5)
Rheumatoid factor	16 (64)	7 (28)	1 (4)	1 (4)	25 (12.4)
Liver function test	19 (32.2)	21 (35.6)	11 (18.6)	8 (13.6)	59 (29.4)
Chest CT scan	17 (39.5)	13 (30.2)	9 (20.9)	4 (9.3)	43 (21.4)
Renal function test	12 (28.6)	16 (38.1)	8 (19.1)	6 (14.3)	42 (20.9)
HLA	17 (63)	7 (25.9)	2 (7.4)	1 (3.7)	27 (13.4)
Urine analysis	10 (29.4)	12 (35.3)	8 (23.5)	4 (11.8)	34 (16.9)
Hepatitis B serology	5 (27.8)	5 (27.8)	5 (27.8)	3 (16.7)	18 (8.9)
Serum calcium	6 (37.5)	6 (37.5)	2 (12.5)	2 (12.5)	16 (7.9)
C-reactive protein	4 (36.4)	2 (18.2)	2 (18.2)	3 (27.3)	11 (5.5)
TB gold	4 (30.8)	4 (30.8)	3 (23.1)	2 (15.4)	13 (6.5)
TORCH	1 (33.3)	1 (33.3)	1 (33.3)	0	3 (1.5)
Toxoplasma titre	1 (25)	3 (75)	0	0	4 (1.9)
MRI brain	4 (40)	4 (40)	2 (20)	0	10 (4.9)
HIV	2 (20)	5 (50)	1 (10)	2 (20)	10 (4.9)
Peripheral blood smear	5 (62.5)	2 (25)	1 (12.5)	0	8 (3.9)
Abdomen ultrasonography	3 (42.9)	3 (42.9)	1 (14.3)	0	7 (3.5)
Interleukin-6	4 (57.1)	1 (14.3)	2 (28.6)	0	7 (3.5)
TSH level	2 (50)	1 (25)	1 (25)	0	4 (1.9)
X ray SI	2 (50)	2 (50)	0	0	4 (1.9)
TPHA	2 (50)	1 (25)	0	1 (25)	4 (1.9)
Anti-CCP	1 (33.3)	1 (33.3)	1 (33.3)	0	3 (1.5)
No investigations	6 (66.7)	2 (22.2)	0	1 (11.1)	9 (4.7)

ESR: Erythrocyte sedimentation rate; VDRL: Venereal disease research laboratory test; ACE: Angiotensin-converting enzyme; ANA: Antinuclear antibody; ANCA: Anti-neutrophilic cytoplasmic autoantibodies; CT: Computerized tomography; HLA: Human leukocyte antigen; TB: Tuberculosis; MRI: Magnetic resonance imaging; HIV: Human immunodeficiency virus; TSH: Thyroid stimulating hormone; TPHA: Treponema pallidum hemagglutination test; Anti-CCP: Anti-cyclic citrullinated peptide.

The most commonly performed investigations were complete blood count (CBC; 90.1%), chest X-ray (CXR; 82.1%), Mantoux test (77.6%) and erythrocyte sedimentation rate (ESR; 73.6%; Table 2). In about 61.7% of patients, investigations undertaken did not contribute to the overall management of uveitis.

The 95.5% of the patients had undergone one or more investigations with an average out-of-pocket expenditure of about 60 dollars (Table 3). The mean cost of relevant investigations was Rs 1706.9±4788.5 and for not relevant investigations was Rs 3666.5±6549.1 with median of Rs 500 in relevant investigations and Rs 1500 for not relevant investigations.

Noncompliance to treatment was noted in 22.4% of patients and this included stopping treatment on their own, delay in initiation of treatment, using eyedrops less frequently than prescribed and failure to shake eyedrops formulated as a suspension (Table 4).

Three-fourths of these patients attributed the non-compliance to a busy work schedule, difficulty in reading that interfered with both work and attendance at school, inability to obtain medicines at their locality and prompt relief of symptoms (Table 5). Poor comprehension of instructions provided by the treating physician as a reason for non-compliance was indicated by 26.7% of the patients.

Table 3 Cost expenditure in relevant and not relevant investigations

Approximate cost (Rs)	*n* (%)
1-1000	93 (46.2)
1001-2000	46 (22.9)
2001-3000	12 (6.0)
3001-4000	3 (1.5)
4001-5000	16 (7.9)
>5001	17 (8.5)
Free of cost	5 (2.5)
No investigations	9 (4.5)
Total	201 (100)

Rs: Rupees.

Table 4 Factors related to non-compliance to treatment

Comment	*n* (%)
Stopped treatment by self	13 (28.9)
Not shaking suspension	11 (24.4)
Less frequency	
<2 times	7 (15.5)
2-4 times	2 (4.4)
>4 times	3 (6.8)
Wrong/no taper	3 (6.8)
Did not initiate treatment	2 (4.4)
Not prescribed treatment	2 (4.4)
Self-medication	1 (2.2)
Mix up of drug	1 (2.2)
Total	45 (100)

Table 5 Reason behind non-compliance to treatment

Reasons	*n* (%)
Incomplete instructions by physician	12 (26.7)
Busy at work/school	10 (22.2)
Poor understanding of drugs side effect	7 (15.6)
Symptomatic relief	6 (13.3)
Difficulty in near vision	4 (8.9)
Drugs not available near residence	2 (4.4)
Lack of access to eye facility	2 (4.4)
Symptoms reappeared	1 (2.2)
Wanted second opinion	1 (2.2)
Total	45 (100)

DISCUSSION

Uveitis is a common sight-threatening inflammatory ocular disease with a variable epidemiology worldwide depending on various factors like host, environmental, genetic, ethnic, and demographic factors[8]. Although patients may present with a plethora of ocular and systemic symptoms and signs, obtaining an etiological diagnosis is difficult for a large majority. Treatment of uveitis can be done rationally only by categorizing the nature of uveitis and then defining the treatment objectives. While obtaining an etiological diagnosis is of utmost importance, one must also refrain from undertaking a long list of laboratory investigations that have no proven utility in assisting this objective. As has been widely recommended, diagnostic investigations should be tailored to match the clinical suspicion and intended therapy. This would prevent excess expenditure by the patients and also avoid the risk of treating patients based on highly prevalent false positive reports, in a given population.

In our study, investigations had been undertaken in 192 (95.5%) patients before presenting to our centre. These tests were able to help identify specific etiology or associations only in 36 patients (17.9%). The investigations were not tailored as per the history and examinations in more than half of the cases (57.2%). The most common investigations done were CBC, CXR, Mantoux test (77.6%), and ESR. CBC, ESR and C-reactive protein (CRP) were found to be within the normal limit in the majority of uveitis patients and were not related to any specific cause of uveitis in an earlier study[9]. CXR was abnormal in only 15% of active uveitis cases in a cross-control study reported by Groen *et al*[10]. It was observed that a few investigations were done multiple times in some cases as they were advised by different physicians. In one of the cases, the Mantoux test was advised 10 times by different physicians. This not only increases cost expenditure for the patient but also leads to misinterpretation of false-positive results and inappropriate treatment. It also indicated the lack of stringent history and evaluation during the workup of patients with uveitis.

In our study, we found that around 14% of patients required more than 60 dollars for additional investigations. In comparison, the cost of investigations for a tailored approach would be about 15 dollars. In a prospective study by de

Parisot *et al*[11] the mean cost of investigation per patient in the standardized strategy was 182.97 Euros and 251.75 Euros in the open strategy for etiological diagnosis of uveitis. It was observed that a standardized strategy was a cost-saving approach for the etiological diagnosis of uveitis.

Compliance-related queries were evaluated in patients who showed no improvement or had worsened on ocular examination at first follow-up. It was seen that 1 in 4 of the patients showing suboptimal response, were not compliant to the treatment. The most common form of non-compliance was patients stopping treatment on their own (28.9%). In more than a quarter of patients (26.7%), poor comprehension and incomplete instructions by the treating physician were attributed as the cause for non-compliance. Some serious issues noted as a result of this have been the development of severe oral ulcers by taking methotrexate tablets daily instead of once a week, instillation of corticosteroid skin ointment instead of eye ointment and continued use of both oral and topical corticosteroids without taper at the suggested time interval. Atreja *et al*[12] described interventions like providing clear instructions and encouraging open and non-judgemental dialogue regarding patients who encountered difficulties with compliance, simplifying treatment regimen, and discussing specifics of their disease, intended treatment goals, and alternative treatment options which could help improve adherence to the treatment. A recent study by Hassan *et al*[13] suggests a patient-centric approach to improve adherence to medications to ensure patients are both motivated and empowered. Patients can also use medication boxes to organize their medications, remember dosing times with the help of alarms, and track treatment over time using smartphone applications[14-15]. Similarly, in patients with uveitis, proper counselling by the treating physician regarding the disease, treatment, and side effects of the drugs is of paramount importance to improve compliance and reduce unexpected adverse situations.

Special emphasis was given to tuberculosis as it was found to be the most common systemic association of uveitis in our study. Owing to the endemic nature of tuberculosis in our country, the mere history of past treatment for tuberculosis does not make it to be an etiological relation[16]. A similar association was seen in an earlier study on 980 consecutive uveitis patients designed to determine the patterns of uveitis presenting to our centre[17]. In addition, in an earlier case-control study on non-syndromic uveitis, syndromic uveitis and central serous chorioretinopathy, the authors found the prevalence of systemic tuberculosis (based on past treatment history) to be no different in the three groups[18]. We have also reported earlier that the positivity of tuberculin skin test and interferon-gamma release assay in patients with serpiginous choroidopathy (an entity often emphasized in literature to be of tubercular etiology), had no correlation to each other[19-20]. In the current study, none of the patients had ocular lesions considered definitive of tuberculosis, like tubercles and tuberculoma. Most patients had a history of being treated for systemic tuberculosis, well before the development of uveitis. Of 6 patients who were taking ATT at the time of this study, 2 were using it for presumed ocular tuberculosis. ATT was discontinued by us in these patients as we did not find substantial evidence linking uveitis to tubercular etiology.

The need for DOTS providers to act as a bridge between the public sector and the private sector has been emphasized[21]. Contrary to this, in our study, only 5 patients prescribed ATT, had been registered under DOTS centres. Nonadherence and non-compliance of physicians to treat patients without DOTS registration are likely to become a barrier to the World Health Organisation achieving the target of eliminating tuberculosis worldwide. The prevalence of adverse drug reactions from ATT in India ranges from 2.3% to 17%[22]. In our study, two patients were reported to have side effects due to ATT drugs. One patient developed hepato-toxicity which was noticed on a follow-up liver function test and another developed optic neuritis due to ethambutol toxicity. ATT was discontinued in them soon after noting the side effects. It is hence also essential to keep patients prescribed ATT, on close follow-up for early recognition of the adverse drug reaction. However, we notice that several studies discussing their results on treatment outcomes following treatment with ATT for uveitis, fail to provide a detailed analysis of documented adverse effects in groups that were lost to follow-up and in those who completed the study.

Though we did not encounter any case with psoriatic uveitis in our study, a special mention regarding psoriatic uveitis seems necessary as it is a distinct clinical entity[23-26]. It has distinguishing clinical features such as higher prevalence in HLA-B27-positive psoriatic arthritis (PsA) patients compared to non-PsA patients, bilaterality in 62% of cases, with prolonged duration of activity (>11wk), requiring the need to add oral non-steroidal anti-inflammatory drugs more often than HLA-B27 associated uveitis. Few studies have been conducted to evaluate the association between uveitis and psoriasis when the joints are not affected. Fortunately, psoriasis without arthropathy does not appear to be a high-risk factor for the development of uveitis. Uveitis is more likely to develop in patients with arthropathy or psoriasis pustulosa compared to other forms of psoriasis, but the presence of HLA-B27 may be associated with more severe uveitis. HLA-B27-positive patients tend to develop a more resistant, recurrent form of uveitis that is more difficult to control. Anterior uveitis is quoted as for 7% to 25% in psoriatic patients with

spondylarthritis[27], with a prevalence of HLA-B27 quoted as for 40% to 50% and two genes (the *Arts1* and *IL23R*) correlated to the ankylosing spondylitis, were detected by the Wellcome Trust Case-Control Consortium Study.

But the HLA-B27 anterior uveitis, associated with more than half of cases (49% to 90% according to Monnet[28]), is often misdiagnosed. So, in accordance with Conti *et al*[29], "PsA is a common immune-mediated chronic inflammatory skin disease that occurs in 2% to 3% of the worldwide population, and includes risks of depression, cardiovascular disease and arthritis", covering the proposed pathogenesis as a "chronic relapsing autoimmune disorder which presents with excessive keratinocyte proliferation, abnormal differentiation, enhanced type I interferon, angiogenesis and over-expression of several chemokines and cytokines which contribute to the disease pathogenesis". PsA iridocyclitis is a correlated pathology observed in early PsA and is not associated with PsA clinical pattern and HLA-B27 positivity[30-31].

In conclusion, our observations suggest that most investigations done for uveitis, in our study cohort, do not seem to be tailored to the clinical workup of the patient. Investigations such as complete hemogram, ESR, and CRP do not contribute to the routine management of uveitis patients and are to be discouraged. In countries wherein tuberculosis is highly endemic, results of tests such as Mantoux and CXR must be viewed with caution and association must not be interpreted as causation. In addition, owing to the strong discordance between Mantoux test and the Quantiferon Gold tuberculosis test and the high risk of false positivity, these tests should not become the sole basis for initiating ATT. In patients showing suboptimal response to treatment, non-compliance was not so infrequent. Adequate counselling by the treating physician or trained counsellors about treatment and side effects of the medicines is likely to improve treatment compliance and prevent disease chronicity.

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