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AN OVERVIEW OF UVEITIS MANAGEMENT APPROACHES

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Abstract:
Uveitis may exist as a clinical manifestation of an underlying systemic disease or may represent an idiopathic entity, sometimes with a very characteristic pattern. Different forms of uveitis have been defined on the basis of three important variables: chronicity, anatomic location, and underlying aetiology. The evolving understanding of the immune system has resulted in a more targeted approach to manage patients with different forms of uveitis, although clearly this approach is at a very early stage. Diagnosis of uveitis is difficult. Etiologic investigations should take into account the epidemiology of uveitis and should focus on the most severe forms of the disease and those which can be treated. This study was undertaken to establish recommendations for the diagnosis of uveitis. We aimed to review the approaches in manage of uveitis, we conducted search through most important electronic databases, searching relevant studies concerning uveitis management. Although these biologic therapies have provided a larger armamentarium to treat uveitis, challenges remain. Uveitis is not a disease, but a manifestation of many potential systemic diseases that may have specific individual therapeutic targets. Identification and characterization of these underlying diseases are not always possible

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INTRODUCTION:

Uveitis is defined as inflammation of the iris, ciliary body, vitreous, retina or choroid. Fundamental studies have shown genetic predispositions, T and B lymphocyte involvement, cytokines and chemokines signatures and signalling pathway also as environmental influences in uveitis [1,2]. Its incidence is 17–52/100,000 person-years and therefore the prevalence is 38–284/100,000 persons [3]. A study of medical insurance claims for 4 million individuals within the USA reported a prevalence of 133/ 100,000 persons, including a predominance of non-infectious uveitis (90.7%) and anterior uveitis (80%) [3,4].

Epidemiologic studies about the distribution of the assorted styles of uveitis and their aetiology are important in helping the clinician to research, diagnose, and manage these pathologies. The results of those studies may provide new insights for research into areas like pathogenesis of uveitis, and should highlight the potential for research on certain specific form of uveitis in numerous regions. Despite the important impact on public health of uveitis, limited knowledge is accessible regarding the epidemiology of this disease [5].

Since 2005, uveitis has been classified anatomically in step with a part of the attention affected (**Fig. 1**), and therefore the rate of onset and course of the disease [4,6]. Uveitis is 'limited' if it lasts for b3 months and 'persistent' if it's present for N3 months, and its onset could also be sudden or insidious. The term acute uveitis is reserved for uveitis which occurs suddenly with a limited course (e.g. anterior uveitis related to histocompatibility antigen (HLA)-B27). Recurrent uveitis is defined as episodes of uveitis separated by periods of remission of N3 months without treatment. Finally, uveitis is taken into account to be chronic if it persists for N3 months or reoccurs b3 months after stopping treatment. The etiologic distribution is directly linked to those factors [7].

Idiopathic anterior uveitis represents the bulk of the cases, over 50% in most of the Western series. the foremost frequent clinical associations in those countries are idiopathic, human leukocyte antigen (HLA)–B27-positive, spondylitis, Fuchs heterochromic iridocyclitis, and herpes. The possession of the HLA-B27 antigen could be a reliable genetic risk factor for acute anterior uveitis, since nearly 55% of Caucasian patients with acute anterior uveitis are HLA-B27 positive compared to 8%-10% of the final population [8,9].

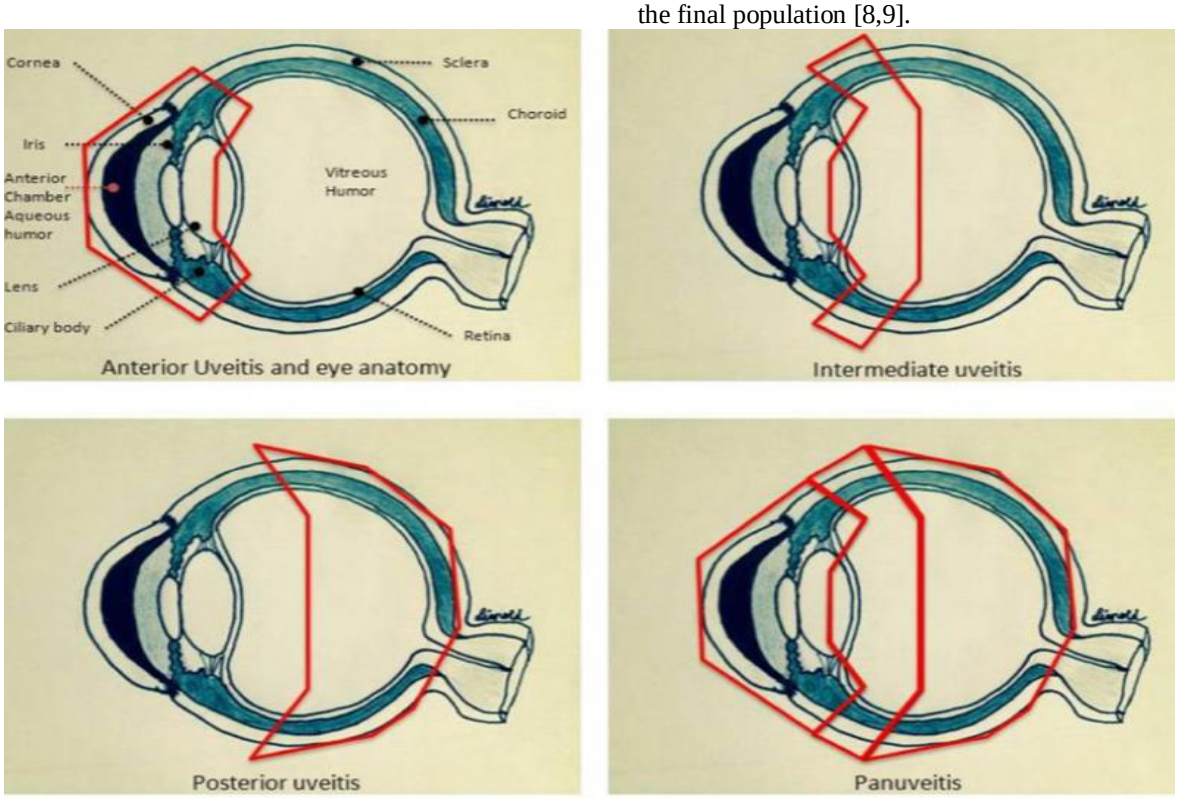

Fig 1: Anatomy of the eye and anatomic patterns of uveitis. Anterior uveitis, intermediate uveitis, posterior uveitis, involvement of all three segments of the eye [7].

In this article, we review most of the published articles on management of uveitis worldwide and discuss novel and interesting information obtained.

DISCUSSION:

Diagnosis:

Only a few retrospective studies, mainly carried out on a small number of patients, have evaluated the usefulness of complementary investigations within the etiologic diagnosis of uveitis. Hadjadj et al. recently reported that complementary investigations were useful for the diagnosis of ocular sarcoidosis, in an exceedingly selected population of 300 patients [10]. The ULISSE study is that the first prospective study to gauge this diagnostic approach (**Fig. 2**) [11]. the primary step during this study consisted of minimal assessment and investigations oriented consistent with clinical data. within the absence of things orienting the diagnosis or a diagnosis following this step, complementary tests determined in line with anatomic variety of uveitis are proposed. This standardized strategy is drawn from the diagnostic strategy proposed by Harper in 2002 [12] and takes under consideration the conclusions of newer studies and therefore the advice of experts, who, for instance, suggest a real understatement of sarcoidosis cases [86]. in step with these investigations and within the absence of a diagnosis, 'open' investigations is also prescribed. a complete of 903 patients were included and randomized within the ULISSE study [11]. After exclusion of patients who withdrew from the study and major deviations from the study protocol, 676 patients were analyzed: 303 within the standardized strategy arm and 373 within the open strategy arm. there have been significantly more women and more cases of acute anterior uveitis within the standardized strategy arm while posterior uveitis was more frequent within the open arm. There was no significant difference within the proportion of diagnoses obtained within the two arms (49.5% for the standardized strategy versus 54.4% for the open strategy), whereas approximately half as many complementary investigations were administered within the standardized arm. within the standardized group, 97% of diagnoses were established following the primary diagnostic step oriented per clinical data (75.7%) or simple paraclinical investigations in step with the anatomic sort of uveitis (21.3%). Invasive complementary examinations (lumbar puncture, bronchial fibroscopy) proposed for chronic uveitis with involvement of the posterior segment or granulomatous uveitis were rarely allotted, because of the tiny number of patients concerned and therefore the reticence of clinicians. the subsequent cases are excluded from these recommendations: paediatric uveitis, immunosuppressed patients [11,12], severe retinal vasculitis and ophthalmologic conditions whose diagnosis depends on an ophthalmologic examination.

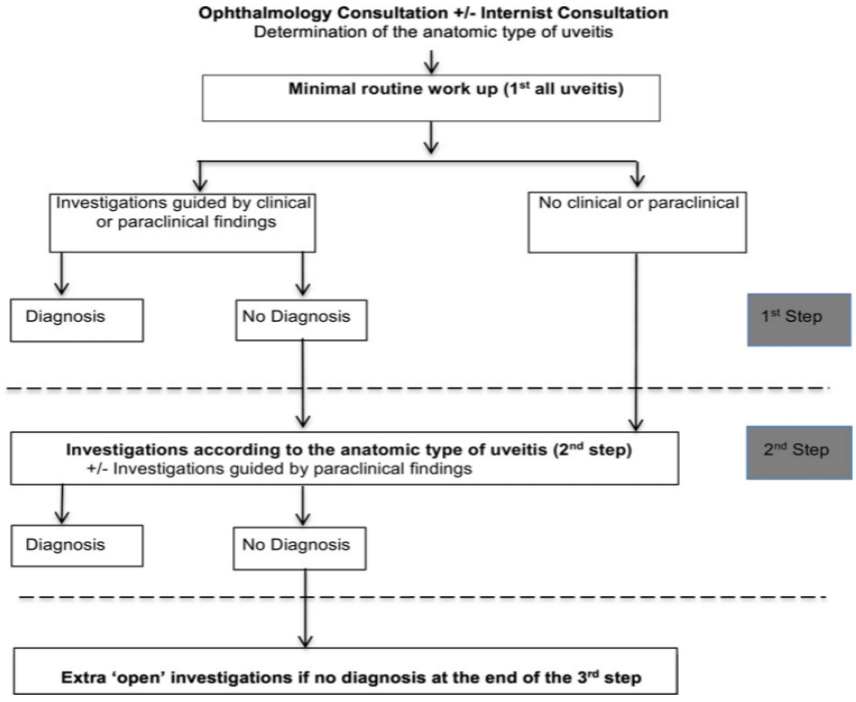

Fig 2: Strategy for the etiologic diagnosis of uveitis. [10]

Treatment approaches:

The therapeutic approach to uveitis requires careful consideration of aetiology, anatomic site involved, chronicity, prior treatment failure, and potential ophthalmic and systemic risks of proposed therapy. Patients with uveitis need to be carefully evaluated by both an ophthalmologist and a physician trained in internal medicine (preferably a rheumatologist or immunologist) to establish a diagnosis and assure that an infectious, primary neurologic, or malignant process is not present, as therapy in these circumstances is very different from that for other forms of autoimmune uveitis.

Nonbiological agent:

The most frequent form of uveitis is acute and anterior uveitis, and also the conditions chargeable for this sort of uveitis generally respond well to topical corticosteroids and cycloplegic and/or mydriatic agents. Patients with chronic disease, intermediate uveitis, posterior uveitis, or panuveitis, who have the best morbidity require aggressive therapy. High-dose systemic steroids are generally the primary therapeutic intervention. The recommended initial therapy is typically prednisone at doses of 40-80 mg per day. In severe cases, parenteral steroids are used, and there are data for “pulse dose” steroids in uveitis.

Methotrexate has been accustomed treat non-infectious uveitis as an oral agent, parenterally and as an intra-ocular injection. it's a folate antagonist that inhibits dihydrofolate reductase. This enzyme is critical within the synthesis of supermolecule, and so methotrexate inhibits rapid cell growth and proliferation [4]. Although studies on both high- and low-dose methotrexate in uveitis are published [6], generally doses between 15 and 25 mg per week orally or parenterally are effective. There are not any prospective, randomized, masked studies evaluating the efficacy of this agent, although it's very frequently used. the information supporting its use are predominantly case series and reviews [8]. In one large retrospective noncomparative interventional case series of 160 patients with differing kinds of uveitis, inflammation control was achieved in 76.2% of patients, steroid-sparing effect was achieved in 56%, and vision was maintained or improved in 90% of patients [6]. Mycophenolate mofetil may be a prodrug of mycophenolic acid, which is an inhibitor of inosine-50 - monophosphate dehydrogenase. This therapy depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits proliferation, thereby suppressing cell-mediated immune responses and antibody formation [9]. Mycophenolate dosing generally requires 2-3 g/day in divided doses. during a retrospective case series that evaluated 84 consecutive patients with inflammatory disease who were treated with mycophenolate, of which 61% had uveitis, the median dose of prednisone at the beginning of mycophenolate mofetil therapy was 40 mg per day. the bulk of the patients (82%) were considered treatment success cases, as judged by the power to manage inflammation and taper prednisone to 10 mg daily [12]. Cyclosporine could be a specific T-cell inhibitor that forms a posh with cyclophilin, which then inhibits the phosphatase activity of calcineurin. This effect regulates nuclear translocation and subsequent activation of transcription factors [13]. Dosing place autoimmune ophthalmic diseases is mostly between 2.5 and 5 mg/kg, and it's administered twice daily, although in some studies, lower doses are used. Cyclosporine has been studied in a very number of uncontrolled trials in various sorts of uveitis [14]. during a larger randomized and controlled study of 96 patients, it succeeded in decreasing the frequency and severity of disease flares [15]. This medication has been used broadly across different autoimmune ophthalmic disease and it does appear to be fairly effective. Tacrolimus, a macrolide antibiotic, although structurally unrelated to cyclosporine A, contains a similar mode of action. It binds to immunophilin, an FK506 binding protein, which then inhibits calcineurin phosphatase [16]. Its dose range is 0.03e0.08 mg/kg/day. in an exceedingly randomized trial of patients with various aetiologies of posterior uveitis comparing cyclosporine to tacrolimus, both groups responded equally. a complete of 13 patients (68%) taking tacrolimus and 12 patients (67%) taking cyclosporine gone through treatment [17]. Azathioprine is an imidazolyl derivative and a prodrug for mercaptopurine, which is incorporated into replicating DNA, blocking the pathway of purine synthesis and thus impeding T and lymphocyte replication [16,17]. during a study of 21 patients with corticosteroid-resistant non-infectious uveitis, who were treated with azathioprine (2.5 mg/kg/day), acuity evaluated resulted in complete success observed in 62.5%, partial response in 20.9%, and failure in 16.6% of patients. Inflammation as an outcome measure after azathioprine treatment resulted in complete success in 70.8%, partial response in 29.1%, and failure in 16.6%. Complete response of steroid sparing was observed in 85.7% of patients and complete success of the three listed criteria was observed in 57.1% of patients [17].

Anti-TNF agents:

The anti-TNF agents are predominantly studied in a very retrospective manner, although some prospective studies have now been successfully completed. Recently, three studies are conducted with adalimumab, with subsequent FDA and EMA approval, for the management of non-infectious intermediate uveitis, posterior uveitis, and panuveitis. Currently, Infliximab, a chimeric mouse/human antibody, is exclusive within the anti-TNF group of therapies in this it's approved for the treatment of the many rheumatic illnesses during a wide selection of doses, thus providing dosing flexibility which will range from 3 mg/kg every 8 weeks to 10 mg/kg every 4 weeks. it's not formally approved for the management of uveitis, although it's frequently used for this group of illnesses. Given the potential impediment of the blood ocular barrier and also the frequent need for high-dose medications to treat ophthalmic disease, this could be a very important advantage. Infliximab has been wont to treat various varieties of uveitis in many systemic illnesses, where uveitis could be a common manifestation, and in patients with idiopathic styles of uveitis. it's been utilized in juvenile idiopathic arthritis (JIA) [18], spondyloarthritis [19,20], colitis, sarcoidosis, and Behcet's disease. In Japan, infliximab is approved for the treatment of Behcet's disease associated uveoretinitis. Prospective data from eight tertiary uveitis centers were analyzed in 50 patients. At 1 year, uveoretinitis had improved in 69%, improved somewhat in 23%, was unchanged in 8%, and had worsened in none. one in all the few prospective studies enrolled 23 patients with various underlying etiologies of resistant uveitis [19,20,21].

Adalimumab, somebody's antibody against TNF approved for the therapy of the many autoimmune diseases, has also been accustomed treat recalcitrant uveitis [18] and has been recently approved for the management of noninfectious intermediate uveitis, posterior uveitis, and panuveitis. during a prospective, multicenter, open-label trial to assess the effectiveness and safety of adalimumab in treating refractory uveitis patients with multiple underlying systemic conditions, 68% of patients were responders at 10 weeks and 39% showed durable response at 50 weeks. No patient experienced treatment-limiting toxicity associated with the study therapy [22,23,24].

In a noteworthy study, comparing infliximab to adalimumab in anterior uveitis, the next benefit for adalimumab was demonstrated. a complete of 48 patients were treated with infliximab and 43 with adalimumab. Fifty-three percent achieved remission, 32.9% had recurrent anterior uveitis, and 11.8% failed to respond. a better remission rate was observed with adalimumab 67.4% versus 42.8% with infliximab (p ¼ 0.025). Caution must be exercised in interpretation of this study, given the trial design and also the indisputable fact that these were patients with only anterior uveitis [18].

CONCLUSION:

The diagnostic approach to uveitis should be adapted to epidemiologic data and to the resources of the healthcare system. Ophthalmologic signs and symptoms observed by ophthalmologists and the findings of the clinical examination (anamnesis, physical examination) are crucial.

The strategy of treating uveitis has also morphed into an approach where early and aggressive intervention is viewed as the therapeutic goal. A recent expert panel has recommended the use of two antiTNF agents, infliximab and adalimumab, as first-line therapy for the treatment of ocular manifestations of Behcet's disease. Clinical trials in uveitis are difficult to perform given the rarity and heterogeneity of this group of illnesses and defining appropriate outcome measures. Uveitis is not a disease, but a phenotypic expression of an abnormality in the immune system.

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