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Inflammatory eye disease: pre-treatment assessment of patients prior to commencing immunosuppressive and biologic therapy: Recommendations from an expert committee

Running title: **Assessment of patients prior to immunosuppression**

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Abstract

Aim

To outline recommendations from an expert committee on the assessment and investigation of patients with severe inflammatory eye disease commencing immunosuppressive and/or biologic therapy.

Method

The approach to assessment is based on the clinical experience of an expert committee and a review of the literature with regard to corticosteroids, immunosuppressive drug and biologic therapy and other adjunct therapy in the management of patients with severe sight-threatening inflammatory eye disease.

Conclusion

We recommend a careful assessment and consultative approach by ophthalmologists or physicians experienced in the use of immunosuppressive agents for all patients commencing immunosuppressive and/or biologic therapy for sight threatening inflammatory eye disease with the aim of preventing infection, cardiovascular, metabolic and bone disease and reducing iatrogenic side effects.

Introduction

Inflammatory eye diseases (IED), such as uveitis and scleritis, are a significant cause of blindness and visual impairment worldwide[1-5]. Although corticosteroids remain the mainstay of initial therapy and are effective in the rapid control of IED, the common occurrence of significant side effects related to prolonged systemic corticosteroid therapy and the loss of disease control as the steroid dose is decreased, often necessitates the use of additional immunosuppressive agents[6]. In addition, a proportion of patients have severe ocular disease that is resistant to corticosteroid therapy[7, 8]. The drugs most commonly used as corticosteroid-sparing agents include : azathioprine, methotrexate, mycophenolate and cyclosporine, whilst tacrolimus and cyclophosphamide are used infrequently[8]. All these drugs are associated with the potential for significant side effects and important drug interactions[9]. Recently, biologic agents, including antibodies against cytokines, such as tumor necrosis factor- α , IL-1 β , IL-6, anti B (anti-CD20) and T cell antibodies like IL-2R,

as well as the cytokine IFN- α have become available to treat patients with uveitis and other inflammatory eye diseases[10, 11].

The aims of immunosuppressive therapy in patients with IED include: the preservation and/or recovery of vision, relief of associated symptoms, and maintenance of the patient's quality of life. Importantly, this should lead to the prevention of complications of their underlying disease combined with prevention of drug-related adverse events and complications, particularly those from unnecessary high maintenance doses of (>7.5 mg/day) corticosteroid therapy[6, 12].

An essential component in achieving these aims is a careful and considered assessment and planning process. Such an assessment would normally be carried out in parallel with investigations into the etiology of the patient's inflammatory eye disease and typically after the commencement of high dose systemic corticosteroid therapy, as the majority of patients present with acute vision-threatening inflammation that requires urgent therapy. There are previous publications and reports of the evaluation and assessment of patients before starting immunosuppressive or biological therapy, although there have been no systematic reviews or expert guidelines developed for patients with IED[8, 13].

The primary objective of these recommendations is to assist ophthalmologists and physicians caring for patients with IED and provide a framework to help guide baseline information gathering about patients prior to commencing systemic immunosuppressive therapy. These recommendations are summarized in Table 1 and are designed for physicians and members of the clinical team caring for patients with IED who require systemic immunosuppressive and/or biologic therapy and are not meant to be prescriptive or essential in all cases. It is the responsibility of the treating ophthalmologist or internist to decide on the appropriate investigations for the individual patient, and such considerations will be based on experience, socioeconomic and geographical considerations, as well as availability of tests and cost.

Methodology

A 12-person panel of physicians and scientists with expertise in ophthalmology, pediatrics, infectious disease, rheumatologic disease, research, and the use of immunosuppressive drugs in patients with IED, drafted the initial recommendations, which were subsequently reviewed by members of an extended panel.

Evidence

Published clinical study results and adopted recommendations from other expert bodies, including the American College of Rheumatology [14](ACR) and Centre for Disease Control (CDC), where relevant. Recommendations were rated according to the quality and strength of available evidence and relevant guidelines developed by other expert committees.

Process

The panel was convened in September 2015 and communicated regularly through March 2016. Subgroups of the panel summarized and presented

available information on specific topics to the full panel; recommendations and ratings were determined by group consensus.

Recommendations

Recommendation 1.

Prior to immunosuppressive or biologic therapy, patients should have a comprehensive and individualized pre-treatment evaluation (Table 2) to prevent or minimize therapy and disease-related complications.

The pre-treatment evaluation of patients with IED is instituted at the time of diagnosis in parallel with diagnostic evaluation and prior to commencing immunosuppressive (IS) therapy. The aims of this pre-treatment evaluation are to establish a baseline of vital organ function; ensure there are no associated systemic inflammatory, malignant, infective, gastrointestinal or psychological disorders that may be reactivated or exacerbated by IS therapy; and evaluate the patient's risk for drug interaction and potential severe treatment-limiting side effects.

Table 2 summarizes an approach to the pre-treatment evaluation of patients with IED prior to commencing systemic IS therapy. It outlines the important considerations, relevant features and investigations to be considered based on a careful clinical assessment. The table is not meant to be comprehensive or to replace good clinical judgment but is intended to serve as a guide to ensure due consideration is given to relevant and important aspects of the management of patients requiring systemic immunosuppressive therapy. The table does not relate to the investigation of patients required to establish an underlying cause for the IED, particularly infectious causes of IED. The development of suitable questionnaires may facilitate the pre-treatment assessment of patients with IED.

Infections that may be exacerbated or reactivated as a result of systemic immunosuppressive or biological therapy include: TB, HBV, HCV and HIV. These infection risks should be assessed or excluded before commencing such therapy. Infections, such as TB, require therapy to allow safe use of IS therapy[13, 15, 16]. The patient's immune status and immunization history are important in planning on-going prevention of infection whilst on immunosuppressive therapy (see recommendation 4).

As most immunosuppressive drugs have the potential to cause or exacerbate hematological problems, it is essential to perform a baseline blood count, including red and white blood cells and platelet counts. Similarly, as most IS drugs are metabolized and/or secreted by the liver and/or kidney, it is essential to ensure there is normal hepatorenal function before commencing such therapy. These organs may also be adversely affected by IS medications, particularly cyclosporine and it is important to measure baseline and on-going organ function during the course of treatment.

Most treatment regimens include chronic use of low dose corticosteroids affecting bone density[17]. Therefore bone densitometry and appropriate supplement with vitamin D and calcium are important considerations to avoid subsequent morbidity[18] (see recommendation 3). Dietary advice is appropriate for patients with diabetes and obesity and patients with a history of gastro esophageal reflux or peptic ulcer disease may benefit from treatment with a proton pump inhibitor.

Evaluating cardiovascular risk factors and endocrine status (e.g. hypertension, obesity, diabetes and thyroid disease) are important as chronic corticosteroid use may also lead to elevation of total cholesterol, glucose intolerance, increased blood pressure and weight gain. Assessment of cardiovascular risk factors in patients with associated systemic disorders, such as systemic lupus erythematosus and rheumatoid arthritis, is especially vital as they are associated with endothelial cell dysfunction and unregulated pro-inflammatory cytokines, resulting in accelerated risk of atherosclerosis and its complications[19].

As an integral part of the initial assessment of the patient, it is important to consider pre-existing or recent malignancy or pre-malignant lesions that may be exacerbated by IS therapy[20]. Although a long term study did not reveal an increased rate of death related malignancies in patients on long term IS therapy for IED a recent study revealed that such patients have an increased risk of skin, cervical and lymphoid malignancies and patients should be screened for the presence of such neoplasms before commencing IS therapy [21, 22]. This is best achieved by a careful history, examination and targeted investigations.

It is important to consider the presence of autoimmunity and/or autoantibodies for two reasons. Firstly, certain autoimmune diseases may be associated with IED (e.g. rheumatoid arthritis (RA), systemic lupus erythematosus [23](SLE), ANCA-associated vasculitis (e.g. Granulomatous Polyangiitis, GPA etc.)) and; secondly, some biological agents, such as TNF inhibitors, rituximab and IFN-alpha, may induce the production of autoantibodies[24]. TNF and IL-6 inhibitors should be avoided in patients with a history of central demyelinating disease and should be used with great caution in patients carrying a risk for demyelination, such as patients with intermediate uveitis[25].

Drug interactions are a critical factor in long-term systemic IS therapy and it is vital that this is evaluated both at the initial assessment and regularly during the patient's treatment program. All IS drugs have significant potential for serious drug interactions, especially when used in combination, and these are outlined in Table 3 for conventional immunosuppressants and in Table 4 for biologic agents[26].

The patient's reproductive capacity and desire to have children should be discussed and evaluated, and potential drug side effects that may interfere with this function should be appraised[9, 27, 28]. This is mainly an issue in alkylating agent therapy, and consideration should be given to sperm or ovum banking. Such patients require referral to a specialist physician or gynecologist.

There are a number of other immunosuppressive drugs, such as methotrexate and mycophenolate, which are contraindicated in pregnant woman[28].

Recommendation 2.

An extended consultative approach to management of patients with associated systemic disease is recommended.

The treatment of patients with severe uveitis is best managed by ophthalmologists experienced in the management of IED, in some circumstances this can be combined with the consultative input from internists experienced in the management of systemic inflammatory disorders and the use of immunosuppressive and biological drugs. Immunosuppressive therapy instituted to treat systemic disease will often control the associated uveitis [8, 11]. In other cases, exacerbation of uveitis may be the first indication that the underlying systemic disease is not under adequate control. Experienced internists can contribute significantly to the management of patients with chronic uveitis and other IED's by detecting and treating malignancies or infections, which may produce a masquerade syndrome or complicate immunosuppressive therapy.

The treatment of patients with IED has undergone significant change in recent times. These changes include: more aggressive and early treatment of patients with immunomodulatory therapy in order to maintain vision and achieve a rapid remission (e.g. in patients with Behcet's disease); the introduction of new immunosuppressive agents that have significantly decreased morbidity; the increasing use of combination immunosuppressive therapy and biological agents in patients with severe and refractory ocular inflammatory disease (e.g. in children with JIA associated uveitis); and the increasing recognition of the potential paradoxical contribution of immunosuppressive therapy to the morbidity of certain inflammatory disease processes through the increased cardiovascular and oncogenic risks associated with their use[21, 29]. The detection and management of such complications requires close collaboration between the treating ophthalmologist and other relevant specialist physicians.

Recommendation 3.

Patients treated with high-dose and prolonged systemic corticosteroids (>3 months) should have a baseline bone density and fracture risk assessment, which should be repeated at regular intervals in patients on long term glucocorticoid therapy. Patients with evidence of significant bone loss and/or osteoporosis should have treatment to prevent further bone loss as early as possible after commencing corticosteroid therapy (Figure 1).

It is important to measure baseline bone density in patients prior to or soon after the initiation of systemic corticosteroid therapy as up to 10% of bone mineral loss may occur in the first 3-6 months of systemic corticosteroid therapy[30, 31]. Pre-existing osteoporosis should be treated to prevent worsening of this disease, as outlined below. Although the 54 month MUST study did not

reveal a high prevalence of osteoporosis in patients treated with systemic corticosteroids it is recommended that the management of osteoporosis or osteopenia in patients commenced on high-dose or prolonged corticosteroid therapy should be treated in accordance with established evidence based guidelines[32]. The American College of Rheumatology (ACR) has developed guidelines for the assessment, prevention and treatment of glucocorticoid-induced osteoporosis[30, 32, 33]. These guidelines were developed by an expert committee and based on available evidence from the literature. As there has been no similar attempt to develop such guidelines for patients with IED, it is recommended that the ACR guidelines be used to help monitor and manage the risk of increased bone loss and osteoporosis. Measures should be implemented as early as possible to decrease the risk of bone loss in patients treated with corticosteroids. An increased risk of fracture has been reported with doses of prednisone or its equivalent as low as 2.5 to 7.5 mg daily[31]. Often, there are no clinical manifestations until there is a fracture. All patients taking any dose of corticosteroid with an anticipated duration of ≥ 3 months require an evaluation, which includes assessment of clinical risk factors for fracture, BMD (dual-energy x-ray [DEXA scan]) of the hip and spine, and measurement of serum 25-hydroxyvitamin D.

Active measures should be employed to decrease bone loss. All patients should be encouraged to do weight-bearing exercises, avoid smoking, excess alcohol consumption and take positive measures to prevent falls (Table 5). Patients receiving any dose of chronic corticosteroid therapy or initiating corticosteroids with an anticipated duration of ≥ 3 months should take calcium (1200 mg daily), and vitamin D (800 IU daily)[30].

It is recommended that men over 50 years and postmenopausal women, who are receiving or are about to commence systemic corticosteroid therapy (any dose for any duration), should receive osteoporosis treatment if one of the following criteria is fulfilled[30]:

- having an established osteoporosis (T-score ≤ -2.5 or history of fragility fracture)
- bearing a risk to develop osteoporosis (T-scores between -1.0 and -2.5)

In centers in which FRAX measurement is available postmenopausal women and men over 50 years who have a low FRAX calculated absolute risk should receive appropriate therapy if they are taking ≥ 7.5 mg/day of prednisone or its equivalent for ≥ 3 months. This approach will vary between countries and recommendations and guidelines issued by different international groups and the availability of DEXA scans and FRAX measurement.

Although estrogen replacement therapy has been demonstrated to prevent bone loss in postmenopausal women receiving systemic corticosteroid therapy, estrogen-progestin therapy is not recommended for the prevention or treatment of osteoporosis in postmenopausal women because of increased risk of breast cancer, stroke, venous thromboembolism and coronary artery disease[30].

Recommendation 4.**Special considerations are essential in the pre-treatment assessment and management of children, pregnant women and older patients.***Children*

Because of the potential risk of growth retardation in children treated with prolonged high-dose corticosteroids, they should have their height and weight recorded on a growth chart that should be kept up-to-date during therapy, by measuring these at each visit[34, 35].

An increasing number of systemic drugs have been used to treat children with severe IED. These include: corticosteroids, methotrexate, azathioprine, mycophenolate, cyclosporine, sulfasalazine and TNF inhibitors. In contrast, cyclophosphamide and other alkylating agents should be avoided in children. There is limited data for some of the newer biological agents and their use in children. The long-term effects on children exposed to these medications have not been extensively studied and such information will be invaluable in informing future therapy in this particular patient group. Appropriate immunization to prevent infections in children is crucial to initial and long-term management and is discussed below[36].

Pregnant women

A number of systemic drugs have been used to treat pregnant women with severe IED. These include: corticosteroids, azathioprine, cyclosporine, sulfasalazine, TNF inhibitors and interferons[28]. Methotrexate, cyclophosphamide, chlorambucil and mycophenolate should be avoided in pregnant women because of teratogenic issues[28]. There is limited data for some of the newer biological agents and their use in pregnancy. Non-steroidal anti-inflammatory drugs should be avoided in pregnant woman as they may result in the premature closure of the patent ductus arteriosus in the fetus.

Women and men wishing to have children

Men and women with childbearing potential should be counseled prior to treatment with cyclophosphamide, chlorambucil, methotrexate and mycophenolate about the risk of infertility, and of premature menopause (primary ovarian insufficiency) in women[28]. Whenever possible, all patients should meet with a reproductive or infertility specialist prior to therapy with cyclophosphamide. Cryopreservation of semen is usually the preferred fertility-preserving measure in men. Women may be offered cryopreservation of embryos or oocytes, although undergoing egg harvesting is often impractical in seriously ill patients.

Older patients

The burden of uveitis in older subjects is higher than previously appreciated. Interestingly, data from 3 studies of causes of uveitis in older patients indicated the disease was most often idiopathic in etiology and that an infectious cause was more prominent in young patients[37-39]. Masquerade syndromes, such as intraocular lymphoma, are more common in older patients[40]. Comorbidities may contribute to severe uveitis in the elderly, including associated autoimmune diseases, cardiovascular disease and diabetes. Older pa-

tients are more susceptible to the effects of systemic therapy, particularly corticosteroid therapy, which may be associated with osteoporosis, diabetes, hypertension, muscle wasting and raised intraocular pressure. There have been no long-term studies of the effect immunosuppressive therapy in older patients and this represents an unmet need in this group of patients[41].

The SITE Cohort Study, the MUST Trials, and several other publications have provided valuable information with regards to the safety and side effect profile of systemic immunosuppressive therapy in adult patients[6, 32, 35, 42-44]. The most commonly used corticosteroid sparing medications, such as azathioprine, methotrexate, mycophenolate and cyclosporine, are associated with an “acceptable” side effect profile. In contrast, alkylating agents, such as cyclophosphamide, have an “unacceptable side effect profile” when used for prolonged periods of time. The SITE and MUST studies also have provided valuable information with regards to the effectiveness of systemic immunosuppression including the surprisingly infrequent occurrence of significant side effects. The data indicates that these drugs are effective and safe for suppressing ocular inflammation if used according to guidelines.

The SITE study indicated a low or negligible risk of malignancy causing death in patients on long-term immunosuppression for inflammatory eye disease[35]. In contrast, a recent Australian study found an increased risk of skin and cervical cancer in patients on long-term immunosuppressive therapy and has implications for the pre-treatment evaluation of patients treated with long-term immunosuppression[21]. The data with respect to biological agents, particularly TNF inhibitors, is promising thus far and these drugs do not seem to be associated with an increased risk of malignancy based on the rheumatological literature[45]. All patients should be evaluated at baseline to assess their risk of exacerbating or developing a malignancy, particularly patients with a recent history of malignancy, such as females with breast cancer. The need for more information with regards to the long-term effects of immunosuppressive therapy, although difficult, is needed and prospective studies, and registry studies to record the prevalence of complications, such as malignancy, should be pursued[29].

Recommendation 5.

Review of infection risk and immunization status should be made prior to commencing systemic immunosuppressive and/or biologic therapy. Established evidence-based international guidelines, such as the CDC guidelines, should be followed in assessing and managing immunization in patients with IED treated with systemic immunosuppressive and biological therapy.

Disease-specific guidelines for immunization and prevention of infections have not been developed for patients with IED and the expert panel recommends that evidence-based guidelines developed by the Centre for Disease Control (CDC) (www.cdc.gov/vaccine/hcp/acip-recs.html) and Infectious Disease Society of America (IDSA) should be followed[46]. Several other expert groups, including the ACR, have developed guidelines for immunization of pa-

tients before and during therapy with immunosuppressive and biologic therapy and these provide helpful information in the management of patients with IED. The principles outlined in the CDC guidelines are summarized in Table 6. In general, and if possible, patients should be vaccinated before commencing immunosuppressive therapy. However, this usually will involve waiting at least a month before being able to start immunosuppressive or biologic therapy after immunization with a live viral or bacterial vaccine and this is not usually possible in subjects with vision threatening disease. Initiation of immunosuppression should *not* be delayed to facilitate vaccination if immediate treatment is needed. VZV is of significant importance in patients on immunosuppressive therapy because of the potential severity of this infection. There have been no published studies of VZV vaccination in patients with IED treated with immunosuppression. An expert panel of the ACR has endorsed the recommendation that VZV vaccination is safe in adults receiving less than 20 mg of prednisone per day or other low-level immunosuppression[47]. Varicella immunization should be administered to patients with chronic inflammatory disorders who are aged ≥ 60 years or who are aged 50–59 years and varicella positive, prior to initiation of immunosuppression or being treated with low-dose immunosuppression. Other live vaccines should *not* be administered to patients with severe IED on IS therapy (Table 6).

Patients with chronic inflammatory disease (such as IED), who are being treated or about to be treated with immunosuppressive agents, should be encouraged to keep their immunization to influenza, pneumococcus, haemophilus and HBV up to date. The Infectious Diseases Society of America (IDSA) recommends that inactivated vaccines, including influenza, should be administered to these patients based on the CDC annual schedule[48].

Any recommended vaccines should not be withheld because of concerns about exacerbation of chronic immune-mediated or inflammatory illness[48]. Prospective studies in children with inflammatory bowel disease (IBD) and uncontrolled studies in patients with chronic inflammatory rheumatic disease, treated with immunosuppressive therapy, indicate that such patients develop an adequate and protective immune response to influenza vaccine[49]. In adult patients with rheumatoid arthritis or SLE the immune response to influenza vaccine was reduced in subjects receiving azathioprine, infliximab and rituximab[50]. Patients were able to tolerate influenza vaccine without serious adverse effects and vaccination was not associated with disease exacerbation. Similarly, in a few studies in which pneumococcal vaccine has been tried in patients with rheumatoid arthritis treated with anti-TNF therapy and methotrexate, a reduced immune response to the vaccine was detected[51]. Patients receiving rituximab also had a reduced immune response. Both groups of patients had similar responses to vaccination with tetanus toxoid. It would be anticipated that patients with severe IED on such therapy would show a similarly reduced response but such vaccines should not be withheld[51].

Recommendation 6.

Evidence-based data and recommendations from expert committees should be used in selecting appropriate systemic therapy for patients with IED and this should inform the pre-treatment assessment.

Extensive experience in the use of immunosuppressive drugs in the treatment of a variety of diseases, particularly systemic rheumatologic and autoimmune/auto-inflammatory diseases, has resulted in significant changes in the therapeutic approaches to severe inflammatory eye disorders. Expert panels have published guidelines for the use of immunosuppressive drugs and biologicals in patients with ocular inflammatory disorders and these recommendations represent a consensus amongst experienced physicians and ophthalmologists[8, 13]. The recommended therapeutic approach is to individualize treatment for patients based on a number of parameters including: the specific ocular syndrome (e.g. Behcet's disease, Birdshot retinopathy etc.), the severity of their eye disease (e.g. anterior or posterior, bilateral and unilateral), age of the patient, associated systemic inflammatory disease (e.g. inflammatory Bowel disease, sarcoidosis), systemic co-morbidities (e.g. diabetes, osteoporosis, renal disease, liver disease, hypertension and heart disease) and the patient's life-style and general preference. Specific therapies necessitate specific pre-treatment assessment and monitoring as outlined in Table 4.

Evidence based information should guide specific IS therapy in well-defined, non-infectious uveitis entities, such as Behcet's disease, systemic vasculitis, sarcoidosis, Birdshot retinopathy and Vogt Koyanagi Disease (VKHD). Although it would be useful to apply evidence-based medicine in the approach to immunosuppressive therapy for inflammatory eye disease, this is not always possible. There are only a few well-controlled, randomized, double-masked trials comparing different immunosuppressive regimens in the treatment of ocular inflammatory disorders[52].

Recommendation 7.

Regular review, monitoring, patient education and preservation of quality of life are an essential component of therapy.

Patients require review at frequent intervals during the early stages of treatment to ensure that they are adequately immunosuppressed, the disease is responding appropriately and they do not manifest any side effects from the immunosuppressive treatment. The clinical response should be assessed and objective measures taken to ensure an adequate disease response is achieved. The lymphocyte count is maintained between 500-1000 cells/ μ l in patients on therapy that induces lymphopenia, such as azathioprine and cyclophosphamide. Patients need to be monitored carefully for drug interactions during the course of their immunosuppressive therapy. Such drug interactions are common, particularly in the elderly [26](see Table 3).

It is often difficult at the outset to establish a time frame for therapy. Therefore the overall aim should be to use the lowest dose of systemic corticosteroids for the shortest possible period of time. Steroid-sparing therapies should be employed with the aim of minimizing the potential for iatrogenic effects and maintain the IED in remission[13, 23]. A study by Kalinina and colleagues indicated that in children with JIA and chronic uveitis a high number of patients

with inactive uveitis relapsed quickly after the withdrawal of MTX . They observed that a longer period of inactivity (2 years) prior to withdrawal and a longer treatment period with methotrexate (3 years) reduced the chance of relapse after drug withdrawal[53].

It is imperative that the physician inform and educate the patient and family, as well as the patient's primary care physician, with regard to the nature of the person's disease, the aims of therapy and the potential for problems associated with immunosuppressive therapy.

Data from QoL studies in patients with uveitis are unfortunately limited, but point to the need for strategies to improve patients' circumstances and to overcome the real and perceived problems associated with a chronic debilitating disease and the effects of systemic immunosuppression[54, 55].

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Table 1
Summary of recommendations

1. Prior to commencing long-term systemic immunosuppressive or biologic therapy, patients should have a comprehensive and individualized pre-treatment evaluation (Table 2) to prevent or minimize therapy and disease-related complications.
2. An extended consultative approach to management of patients with associated systemic disease is recommended.
3. Patients treated with high-dose and prolonged systemic corticosteroids (>3 months) should have a baseline bone density and fracture risk assessment, which should be repeated at regular intervals in patients on long term glucocorticoid therapy. Patients with evidence of significant bone loss and/or osteoporosis should have treatment to prevent further bone loss as early as possible after commencing corticosteroid therapy (Figure 1).
4. Special considerations are essential in the pre-treatment assessment and management of children, pregnant women and older patients.
5. Review of infection risk and immunization status should be made prior to commencing systemic therapy. Established evidence-based international guidelines, such as the CDC guidelines, should be followed in assessing and managing immunization in patients with IED being treated with systemic immunosuppressive and biological therapy.
6. Evidence-based data and recommendations from expert committees should be used in selecting appropriate systemic therapy for patients with IED and this should inform the pre-treatment assessment.
7. Regular review, monitoring, patient education and preservation of quality of life are essential components of therapy.

Table 2
Inflammatory eye disease pre-treatment assessment for patients requiring immuno-suppressive treatment and or biologicals

Clinical	Relevant history and clinical assessment	Investigations, if indicated
Infections to be excluded to prevent reactivation or exacerbation	Hepatitis, sexually transmitted infections (STI), dental disease, human papilloma virus cervical infection, past history of or exposure to tuberculosis (TB).	HIV, HBV, HCV, VDRL, TB (Chest X-ray if clinically required), Skin tests or QuantiFERON-TB Gold test for TB. Pap smear and HPV examination.
Hematology	History of anemia, leukopenia, bleeding disorders and thrombosis.	FBC/ESR/CRP. Anti-cardiolipin antibodies ACL) and β 2-microglobulin.
Metabolic	Renal, liver, endocrine or metabolic disease including obesity	Blood sugar level (BSL), lipids, urea/creatinine, electrolytes, Liver Function Tests (LFT's), urinalysis, uric acid. Thiopurine Methyltransferase (TPMT) test before use of azathioprine.
Bone disease	Age >60 years and post-menopausal woman. Previous corticosteroid therapy. Osteopenia or fracture.	Bone densitometry (DEXA scan). Calcium, vitamin D. Assess fracture risk.
Vascular risk	Hypertension, hyperlipidemia, diabetes, IHD, vascular disease.	Blood pressure, lipids, BSL, C reactive protein (CRP). Doppler, if clinically indicated.
Neoplasia	Previous malignancy or present skin, cervical tumors, lymphoma Abnormal Pap smear (HPV).	Examine skin, cervix, lymph nodes/spleen etc. Pap smear (HPV).
Autoimmune (biologicals)	Autoimmune disease features, particularly before use of biologics. Symptoms suggestive of demyelinating illness	ANA, ENA, DNA, ACL (B2 GPI), ANCA. Urine test for blood, casts and protein. Immunoglobulins and Immunolectrophoresis. MRI brain- particularly in patients with intermediate uveitis.
Medications	Existing therapy, drug interactions, drug allergies and adverse reactions.	Check for interactions and allergy-IgE specific tests and skin tests only if allergies are reported.
Immunization /vaccination	Immunization history, immune status and need for pre-immunosuppression vaccination.	Serology tests for specific infections (HBV, VZV, pneumococcus).
Special risk groups	Children - drug dosages, immunization and long-term effects. Pregnancy and planned pregnancy – contraception, lactation and teratogenicity risk. Elderly - co-morbidities, poly-pharmacy and drug interactions.	Growth charts for children. Check - drug dosage, interactions and teratogenicity. Pregnancy test - if appropriate. Fertility testing and sperm/ova storage - if indicated in treatment with alkylating agents.

Abbreviations: HIV human immunodeficiency virus, HBV hepatitis B virus, HCV hepatitis C virus, TB Tuberculosis, HPV human papilloma virus, FBC full blood count, ANA antinuclear antibody, ANC anti-neutrophil cytoplasmic antibody, VZV Varicella zoster virus.

Table 3
Immunosuppressive Drugs for Inflammatory Eye Disease

Class	Generic Name	Initial Dose	Mechanism	Onset of Action	Drug interactions	Common Side Effects	Investigations and monitoring
Anti-metabolites	Azathioprine	1 mg/kg/day increasing to 2-3 mgm/Kg/day as a single or multiple doses	Alters purine metabolism and inhibits CD28 signaling	1-3 months	Mycophenolate Warfarin ACE inhibitors Co-trimoxazole Allopurinol Sulfasalazine	Bone marrow suppression (leukopenia, thrombocytopenia), GI upset, hepatitis PNP deficiency	Initial TMPT level FBC - baseline; 1, 2, 4 then 8 weekly U/E/Cr and LFTs - baseline; 1, 2 then 4 weekly
	Methotrexate	10-25 mg/wk. Oral, subcutaneous or intra muscular injection	Inhibits dihydrofolate reductase	2 weeks to 3 months	Alcohol, Antibiotics Cyclosporine NSAID Probenecid Sulfasalazine Co-trimoxazole	Bone marrow suppression, stomatitis, hair loss, nausea/vomiting, GI upset, hepatotoxicity (hepatitis, cirrhosis), pneumonitis, fetal loss	FBC - baseline; 2, 4 then 8 weekly U/E/Cr and LFTs - baseline; 1, 2 then 4-8 weekly
	Mycophenolate (-mofetil or -Na) Cellcept	500 mg BID increasing to 1gm BD	IMP dehydrogenase inhibitor (purine synthesis)	2 weeks to 3 months	Azathioprine, antacids; sevelamer, Probenecid; PPIs; antibiotics (excluding co-trimoxazole)	Diarrhea, nausea, neutropenia, infection	FBC - baseline; 2, 4 then 4-8 weekly U/E/Cr and LFTs - baseline, 2 then 4-8 weekly
T-cell inhibitors	Cyclosporine	3-5mg/kg/day (divided dose)	Inhibits calcineurin and thereby inhibits NFAT and IL-2 synthesis	2-6 weeks	Anti-inflammatory drugs; antibiotics; anticonvulsants sirolimus; diuretics; erythropoietin; HMG-CoA reductase inhibitors, statins; nephrotoxic drugs- including tacrolimus, NSAIDs, methotrexate, vancomycin, aminoglycosides amphotericin B, ciprofloxacin, melphalan, trimethoprim (+ sulfamethoxazole), colchicine; Ca-channel block-	Renal dysfunction, tremor, hirsutism, hypertension, gum hyperplasia	FBC - baseline; 2, 4 then 8 weekly U/E/Cr and LFTs - baseline; 1, 2 then 4-8 weekly

					ers; grapefruit juice; corticosteroids; digoxin; etoposide; repaglinide; macrolides; azole antifungals; amiodarone; allopurinol; sulfadimidine; hepatic enzyme inducers; CYP3A4 inhibitors (i.e. carbamazepine, St John's wort)		
	Tacrolimus	0.15mg/kg/bd Increasing to 2-3 mgm bd	Inhibits calcineurin and thereby inhibits NFAT and IL-2 synthesis	2-6 weeks	Similar to cyclosporine aminoglycosides, gyrase inhibitors; potassium sparing diuretics e.g., amiloride, spironolactone, triamterene sirolimus; Ca channel blockers CYP3A4 inducers (e.g. carbamazepine, St John's wort) contraceptives; NSAIDs; highly protein bound drugs (e.g. oral anticoagulants), CYP3A4 inhibitors, e.g. grapefruit juice antifungals (e.g. ketoconazole), HIV protease inhibitors clarithromycin, clotrimazole, erythromycin, omeprazole	Nephrotoxicity, high BP, neurotoxicity, hyperkalemia, hypomagnesaemia, hepatitis, diabetes, tremor.	FBC - baseline; 1, 2, 4 then 8 weekly U/E/Cr and LFTs - baseline; 1, 2 then 4 weekly
Alkylating agents	Cyclophosphamide	1-2 mg/kg/day as oral medication. Can also be used as IV pulse therapy.	Cross links DNA and interferes with replication and cell division	2-8 weeks	Inducers of liver enzyme such as phenobarbitone, imipramine, phenothiazines, hypoglycemics; phenytoin; benzodiazepines; cytotoxics, immunosuppressants; digoxin; Mesna; corticosteroids; anticoagulants; live vaccines; alcohol; grapefruit juice;	Bone marrow suppression, infection, hematuria and hemorrhagic cystitis, increased risk of malignancy, sterility, alopecia	FBC - baseline; 1, 2, 4 then 8 weekly U/E/Cr and LFTs - baseline; 1, 2 then 4-8 weekly
	Chlorambucil	0.1 mg/kg/day	Cross links DNA and interferes with replication and cell division	4-12 weeks	Phenylbutazone; epileptogenic drugs; live vaccines; purine nucleoside analogues	Bone marrow suppression, infection, increased risk malignancy, sterility	FBC - baseline; 1, 2, 4 then 8 weekly U/E/Cr and LFTs - baseline; 1, 2 then 4-8 weekly

Table 4
Biologics and Inflammatory Eye Disease

Class	Generic Name	Initial Dose	Mechanism	Onset of Action	Common Side Effects	Investigations
TNF Blockers	Infliximab	5 mg/kg/ IV over 2 hrs, at 0, 2 and 6 weeks	Binds soluble and membrane-bound TNF α	10 weeks	Injection site and infusion reactions, bacterial infections, reactivation of TB, headache, demyelination, rash, abdominal pain, diarrhea, respiratory infections, ANA and DNA antibodies.	FBC - baseline; 4 then 8 weekly U/E/Cr and LFTs - baseline; 2 then 8-12 weekly
	Adalimumab	40 mg/2wks SC	Binds soluble and membrane-bound TNF α	2-16 weeks	Injection site reactions, bacterial infections, reactivation of TB, headache, rash, abdominal pain, demyelination, diarrhea, respiratory infections, ANA and DNA antibodies.	FBC - baseline; 4 then 8 weekly U/E/Cr and LFTs - baseline; 2 then 8 weekly
	Etanercept	50 mg weekly	P75 TNF receptor fusion protein bivalent binding of TNF	4-8 weeks	Injection site and infusion reactions, bacterial infections, reactivation of TB, headache, demyelination, rash, abdominal pain, diarrhea, respiratory infections, ANA and DNA antibodies. May induce uveitis.	FBC - baseline; 4, then 8 weekly U/E/Cr and LFTs - baseline; 4 then 8 weekly
Interferons	Interferon- α 2b	3-6 million IU/day SC 1-3 times per week	Promotes Treg development up regulates TGF- β , IL-1R antagonist, soluble TNFR	2-4 weeks	Injection site reactions, flu-like symptoms, depression and suicidal ideation. Leucopenia and abnormal liver function tests. Thyroid and SLE autoantibodies.	FBC - baseline; 4 then 8 weekly U/E/Cr and LFTs - baseline; 2 then 8 weekly
	Interferon- α 2a	3-6 million IU/day SC 1-3 times per week	Promotes Treg development up regulates TGF- β , IL-1R antagonist	2-4 weeks	Injection site reactions, flu-like symptoms, depression and suicidal ideation. Leucopenia and abnormal liver function tests. Thyroid and SLE autoantibodies.	FBC - baseline; 4 then 8 weekly U/E/Cr and LFTs - baseline; 2 then 8 weekly
IL-1R Blocker	Anakinra	1 mg/kg/day SC	Competitively inhibits IL-1 binding to IL-1R	4 weeks	Injection site reactions, decreases in neutrophil count, increased infections	FBC - baseline; 4 then 8 weekly U/E/Cr and LFTs - baseline; 2 then 8 weekly

	Canakinumab	Adults >40kg 150 mg S/c 8-weekly	Competitively inhibits IL-1 binding to IL-1 β	4 weeks	Injection site reactions, decreases in neutrophil count, increased infections, headache, vertigo, weight gain, nausea, diarrhea, myalgia, pharyngitis	FBC - baseline; 4 weeks then 8 weekly U/E/Cr and LFTs - baseline; 2 then 8 weekly
IL-6 Blocker	Tocilizumab	4-8 mg/Kg every 4 weeks	Competitive inhibitor of IL-6 receptor	4 weeks	Increased cholesterol, ALT, AST, headache, vertigo, hypertension, infections, diverticulitis and gut perforation.	FBC - baseline; 4 weeks then 8 weekly U/E/Cr and LFTs - baseline; 2 then 8 weekly
CD20 Blocker	Rituximab	375 mg/m ² IV 0, 2 weeks and then as required	Binds to the CD20 antigen on B cells	3-4 months	Infusion reactions, infections, cytopenias. Delay up to 3-4 months in onset of action.	FBC and T & B cells - baseline; 4 then 8 weekly U/E/Cr/Immunoglobulins and LFTs - baseline; 4 then 8 weekly
Plasma Product	Intravenous immunoglobulin (IVIG)	400 mg/kg/day for 5 days and then monthly	Suppresses T and B cell responses	4-8 weeks	Infusion reactions, delayed infusion reactions, headache. Anaphylaxis particularly in patients with anti-IgA antibodies.	FBC - baseline; 4 then 8 weekly U/E/Cr and LFTs -baseline; then 8 weekly

TNF = Tumor necrosis factor, Treg = Regulatory T cell, IL-1R = Interleukin-1 receptor, TNFR = Tumor necrosis factor receptor, BID = twice daily; BP = blood pressure; GI = gastrointestinal; IM = intramuscular; IV = intravenous; LFTs = liver function tests; PO = orally; Q = every; SC = subcutaneously; U/E/Cr = urine, electrolytes, creatinine, FBC= Full Blood Count.

Table 5**ACR recommendations for life style modification and assessment of patients starting systemic glucocorticoids[30]**

Smoking cessation
Decreased alcohol intake (<2 standard drinks/day)
Weight bearing exercises should be encouraged
Calcium and vitamin D measurement and intake
Baseline dual x-ray absorptiometry
Fall risk assessment especially in older subjects
Baseline height measurement
Assessment of prevalent fragility fractures
Spinal radiology for patients on >5 mg of prednisone or equivalent

Table 6
Vaccination of patients with IED on immunosuppressive medications based on CDC guidelines*

Vaccine	Prior to starting immunosuppression (>1 month)	Low-level immunosuppression patients receiving: prednisone <2mg/kg/day methotrexate <0.4 mg/kg/week azathioprine <3 mg/kg/day	High-level immunosuppression patients receiving: greater than low-level criteria or TNF inhibitors or rituximab
Influenza (inactivated)	Usual immunization regimen	Usual	Usual
Hepatitis A	Usual	Usual	Usual
Hepatitis B	Usual	Usual	Usual
DPT	Usual	Usual	Usual
HPV	Usual	Usual	Usual
H. Influenza	Usual	Usual	Usual
Meningococcal conjugate	Usual	Usual	Usual
Pneumococcal PCV13	Recommended >6 yrs. of age	Recommended >6 years of age	Recommended >6years of age
Pneumococcal PPSV23	Recommended ≥2 yrs. of age	Recommended ≥2 years of age	Recommended ≥2 years of age
Polio (inactivated)	Usual	Usual	Usual
Rotavirus- live	Usual	Contraindicated	Contraindicated
Varicella- live	Usual	Contraindicated	Contraindicated
MMR-live	Usual	Contraindicated	Contraindicated

* www.cdc.gov/vaccine/hcp/acip-recs.html

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Figure 1

