Immunosuppressive therapy for chronic uveitis: optimising therapy with steroids and cyclosporin A

Andrew D Dick, Mohammed Azim, John V Forrester

Uveitis denotes inflammation of the uveal tract of the eye and is generally categorised as either anterior (involving the iris/ciliary body) or posterior (involving the choroid as well as adjacent structures including pigment epithelium and retina). Although uveitis is a known cause of blindness, until recently there were few data reflecting the prevalence and incidence of uveitis among the blind, mainly because of the lack of information concerning the incidence of sight threatening complications from uveitis. One recent study has shown that the incidence of visual impairment in uveitis is 35% and is mainly due to posterior uveitis, largely as a result of persistent cystoid macular oedema. Other studies have shown that there is a 25% loss of vision in 4% of patients with anterior uveitis, 43% with posterior uveitis, and 40% with panuveitis. Moreover, specific uveitic syndromes—for example, Behcet’s disease and serpiginous chorioretinopathy, have a renowned poor prognosis without therapy. Suttorp-Schulten and Rothova have highlighted the socioeconomic impact of blindness due to uveitis, especially as most cases of visual impairment occur in the working age group, and uveitis now ranks with diabetic retinopathy as one of the major causes of visual handicap in this age group. As many uveitic entities are curable, or at least controllable in the sense that ocular damage can be prevented or limited with early and adequate therapy, we discuss a structured and rational approach to immunosuppression with respect to the control of intraocular inflammation, which aims to maintain best possible visual function while minimising therapy induced side effects, in particular those which occur with prolonged steroid therapy.

Immunopathogenesis: directing therapy

Fifty per cent of cases of uveitis are classified as idiopathic while many of the others are associated with or form part of other disease entities. However, before considering and commencing immunosuppressive therapy for uveitis, direct infectious causes must be excluded so that appropriate therapy can be commenced. Therefore, management of endogenous posterior uveitis depends on both clinical and associated laboratory based investigations to exclude any infectious aetiology. Many cases of infectious uveitis are clinically obvious—for example, opportunistic infections in immunocompromised individuals (especially in association with HIV) are increasingly frequent causes of uveitis, the treatment of which is highly dependent on specific antimicrobial therapy. In non-immunocompromised individuals, toxoplasmosis (depending on which country and region) is one of the leading causes of uveitis, and although immunosuppression is used to treat this condition it must be used in conjunction with appropriate antibiotic therapy to reduce the incidence of disease relapse. In certain cases, however, differentiation between infectious and non-infectious endogenous posterior uveitis (EPU) may be more difficult. For example, Lyme disease, miliary tuberculosis, or progressive outer retinal necrosis (PORN), may present with signs identical to those of EPU and, despite adequate clinical assessment, immunosuppressive therapy may have already been started on the basis that the condition was considered non-infectious. In these cases, as well as possible ‘masquerade’ conditions such as ocular lymphoma a failure to respond should be a warning sign that the diagnosis may be incorrect and needs to be reviewed. Patients with true EPU are assumed to be autoimmune in nature, and the aim of this review is to focus on the treatment of these primary immune mediated conditions.

IMMUNE MECHANISMS IN UVEITIS

Endogenous anterior and posterior uveitis are clinically and pathogenetically distinct diseases. Most cases of anterior uveitis are acute, self limiting diseases that respond rapidly to therapy and are probably mediated by major histocompatibility complex (MHC) class I/CD8+ cytotoxic mechanisms. In contrast, endogenous posterior uveo-retinitis (EPU) comprises chronic, relapsing disorders that progressively damage vision and are MHC class II/CD4+ T cell mediated diseases. There is clinically a degree of overlap in presentation and course of disease—for example, juvenile rheumatoid arthritis and EPU, despite the pathogenic differences. However, in either condition if significant sight threatening disease is present a common approach of immunosuppression, as we will discuss, should be commenced. While there is no definitive evidence that putative target (auto)antigens, which include S-antigen (S-Ag) and interphotoreceptor retinoid binding protein (IRBP), are directly involved in the induction of EPU, the experimental models have shown that EPU is initiated by antigen specific CD4+ T cells and can be inhibited by the immunosuppressant cyclosporin A (CsA). Furthermore, in EPU activation of peripheral T cells and other markers of immune activation can be detected. Compellingly, there is preliminary evidence that oral tolerance with S-Ag may suppress human EPU. Currently, however, the most specific and successful method of treating non-infectious EPU is immunosuppression based on inhibiting the activation of CD4+ T cells with CsA as documented several years ago.

Non-infectious EPU may occur in isolation or as a feature of systemic autoimmune disease—for example, systemic vasculitis, systemic lupus erythematosus, polyarteritis nodosa, seronegative spondyloarthritides, Behcet’s disease, sarcoidosis, multiple sclerosis, to name a few. Immunosuppression in these circumstances must be tailored to treat both the ocular disease as well as systemic
disease. Successful immunosuppression for ocular inflammation in these conditions will be achieved using the same approach as for idiopathic EPU, especially if the systemic component is quiescent. However, the treatment of sight threatening ocular disease does not depend on whether there is systemic signs of disease or not and should not be governed by the presence or absence of clinical signs. If a significant systemic component is present then immunosuppression must be tailored to treat both ocular and systemic signs.

**Indications for treatment of endogenous posterior uveitis**

**WHAT TO TREAT?**

The appropriate treatment and choice of immunosuppressive therapy for uveitis depends on both the extent and severity of the inflammatory process. Firstly, it is important to establish whether immunosuppression is necessary and, secondly, whether the patient’s general medical condition can tolerate immunosuppression. Although numerous reports on the management of idiopathic uveitis describe the use of immunosuppressive therapy, ranging from orbital floor steroids and systemic steroids to newer agents such as CsA and other cytotoxic agents, the long term use of immunosuppressants by ophthalmologists is still not widespread for several reasons:

- many cases in which steroids have been tried are considered ‘treatment failures’ or non-responders, when relapse occurs on lowering the dose or when significant side effects occur after prolonged use. Such cases are not, in fact, treatment ‘failures’ since steroid therapy was effective albeit at an unacceptably high dose. However, they do highlight the fact that steroids are not appropriate immunosuppressives in the long term.
- many patients are treated too late when visual recovery is unlikely owing to apparent retinal and/or optic nerve damage. Immunosuppressive therapy thus acquires a reputation for being ineffective. Despite this, it is remarkable how often an irreversibly ‘damaged’ macula may recover some function.
- apart from distinct uveitic syndromes where immunosuppression has been shown to be beneficial—for example, retinal vasculitis and Behçet’s disease, the majority of cases are not easily grouped into such classic diagnoses and the nature of their sight threatening disease is not recognised.

EPU represents a spectrum of autoimmune ocular inflammatory disease normally manifesting a set of clinical features—namely vitritis, chorioretinitis, retinal vasculitis, macula, and disc oedema and less commonly retinochoroidal neovascularisation. The severity and distribution of these clinical features will determine both whether to and which immunosuppressive(s) to commence. Since EPU is immune mediated and generated systematically attempts to treat unilocular disease with, for instance, periocular steroids alone will lead to less than optimal control of disease thus prolonging any damaging effects in the affected eye and possibly permitting an earlier onset of disease in the fellow eye by failing to suppress systemically activated cytotoxic T cells.

The decision to treat is determined therefore by the severity of inflammation, classified according to the extent and degree of inflammatory eye signs as minimal, mild, moderate, and severe. The features which characterise these grades are described below, and are based on detecting ‘sight threatening’ inflammation:

- **minimal disease** occurs when there are one or two of the cardinal features of inflammation (see above), such as occasional chorioretinal infiltrates (white dots), minimal or no peripheral vasculitis, and minimal vitritis. The macula/optic nerve is not involved at this stage.
- **mild disease** occurs when there are more signs of inflammation and these are more extensive—for example, focal active vasculitis, more numerous chorioretinal infiltrates, and vitritis. The macula and optic nerve again are not involved at this stage.
- **moderate disease** is present when most of the inflammatory features such as dense vitritis are present and, in addition, there is involvement of or imminent threat to the macula or optic nerve. Significant retinal vessel inflammation is usually present. Sight is threatened or already impaired because of, for example, macular oedema. It is important to recognise that sight threatening disease, involving the optic nerve and macula, may be present without many other ocular inflammatory signs.
- **severe disease** is characterised by extensive changes in any of the cardinal features all of which are present—in particular, chorioretinal inflammation, retinal vasculitis (especially arteritis), optic neuropathy, and vitritis. Vision is usually impaired but may still be normal although under imminent threat because of active macular and/or optic nerve disease.

**WHEN TO TREAT**

Treatment should be commenced when sight threatening inflammation is present—for example, optic nerve swelling and central retinal vasculitis in Behçet’s disease, active serpiginous lesions threatening the fovea, a large central choroidal lesion in multifocal choroiditis, cystoid macular oedema in intermediate uveitis, or a subretinal neovascular membrane in ‘ocular histoplasmosis’. With respect to the clinical signs and stages of intraocular inflammation described above, the threat to sight may be considered to be remote, possible, probable, or likely, and this will determine not only when it is appropriate to commence immunosuppressive therapy but also how quickly and which agents to use.

**Therapeutic options for treatment of endogenous posterior uveitis**

Experimentally there are many routes whereby EPU can be suppressed, inhibiting either the afferent or the efferent immune response. These novel approaches presage a future for more specific therapy for EPU. Some of these approaches are already used for refractory cases of autoimmune diseases—for example, monoclonal antibody therapy directed against CD4+ T cells for rheumatoid arthritis and uveitis (CDw52 (Campath)) and tumour necrosis factor (TNF) cytokine receptor fusion protein of deleting anti-TNF monoclonal antibodies for rheumatoid arthritis. Although in their infancy these developments are increasing the range of possible treatments which have the potential to secure longer term immunoregulation, and may be directed toward ophthalmic use (see below).

Clinically, the mainstay of immunosuppressive therapy for EPU over the past two to three decades has been systemic steroids, but treatment schedules have been erratic and prolonged therapy has rarely been possible because of severe side effects. Despite significant toxicity induced by immunosuppressants during the past 12 years CsA has been used for the treatment of EPU with significant benefit. CsA arguably represents the drug of choice for the long term treatment of sight threatening EPU, because with judicious use toxicity can be minimised. The fellow eye by failure restrict early use of CsA in favour of other immunosuppressives. In the following sections a brief discussion of the main immunosuppressive drugs used for EPU is presented.
Corticosteroids

Steroids may be administered by several routes and traditionally unilocular, mild intraocular inflammation is treated with orbital floor steroids since it is thought that systemically induced side effects can be avoided. However, steroids administered by this route are absorbed systematically, producing serum levels comparable with those achieved with 50 mg of oral prednisolone and not adequate to control inflammation long term. Toxicity with orbital floor steroids is undoubtedly less but mainly for dose related reasons and not because of reduced absorption. Although others use orbital floor steroids we believe that systemic (oral) steroids are usually required for safe control of mild/moderate ocular inflammation whether the disease is unilateral or bilateral. High dose steroids are also effective for the short term treatment of severe inflammation. However, as Howe et al showed patients with EPU require therapy for at least 12 months to maintain control with a high incidence (50%) of side effects (18% therapeutically significant) while 40% required additional immunosuppression. Therefore, long term treatment of EPU with steroids alone has to be viewed with considerable caution as the therapeutic window which avoids side effects without the risk of relapse is small even though corticosteroids and cyclosporin are equally effective when used as monotherapy for mild to moderate disease.

Table 1 presents a retrospective review of a cohort of patients treated at Aberdeen Royal Hospitals NHS Trust from 1992 to 1996, with either prednisolone alone, or combined with CsA or CsA and azathioprine. Within each group, patients presented with varying diagnoses of EPU. Figure 1 shows the visual recovery in 36 patients who on presentation had mild or moderate ocular inflammation and a mean visual acuity at presentation of 6/12 (in 35/53 eyes) and were treated with a reducing course of prednisolone and then a maintenance dose of 10 mg/day or less. In the majority of patients either visual recovery was observed or acuity was maintained (37/53 affected eyes) and in 33 patients steroids were eventually stopped while maintaining post-treatment vision.

CsA was first introduced for the prevention of renal allograft rejection. CsA is a powerful immunosuppressant which works by inhibiting calcium dependent T cell receptor (TCR) mediated signal transduction and thus activation of T cells. This also leads to a down regulation of IL-2 gene transcription and IL-2 receptor expression. Since the initial reports indicating that CsA suppressed EAU and the later demonstration of its clinical value in treating steroid and cytotoxic resistant intraocular inflammation, it has now been used for the treatment of most forms of EPU.

Figure 2 shows the response of treatment of patients with moderate or severe intraocular inflammation (see above) treated with combined low dose CsA (5 mg/kg/day) and prednisolone (<10 mg/day), where after initial control of inflammation with steroids, 42/54 affected eyes improved or maintained Snellen visual acuity with CsA. In this group 31/54 affected eyes presented with 6/12 or worse vision, reflecting the severity and ‘sight losing’ nature of the inflammation which necessitated prolonged therapy for which long term steroid use alone would have required doses well within the toxic range.

Antimetabolites and cytotoxic agents

Several different cytotoxic immunosuppressive agents have been used to treat EPU. These agents include azathioprine, a purine antagonist, antimetabolite, which may be used either as an alternative to CsA in combination with steroids or in addition to CsA and steroid therapy. Methotrexate, which is a folic acid antagonist.

Table 1 Summary of diagnosis and treatment regimens in a cohort of patients with endogenous posterior uveitis at the ocular inflammatory clinics in Aberdeen. A diagnosis of idiopathic consists of patients with undefined posterior uveitis and panuveitis, which includes diagnosis such as presumed ocular histoplasmosis syndrome and others where posterior segment features continually change or cannot be specified to other diagnostic descriptions (for example, overlap syndromes).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prednisolone only</th>
<th>Prednisolone and cyclosporin A</th>
<th>Prednisolone, cyclosporin A, and azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) SD</td>
<td>48 (17.4)</td>
<td>44.6 (13.6)</td>
<td>46.2 (19.9)</td>
</tr>
<tr>
<td>Mean maintenance dose</td>
<td>8.1 (3.1)</td>
<td>7.1 (3.8)</td>
<td>9 (5.3)</td>
</tr>
<tr>
<td>Mean duration of therapy (months)</td>
<td>17.3 (12.0)</td>
<td>20.4 (13.7)</td>
<td>9.5 (13.4)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>RV=5</td>
<td>MFC=4</td>
<td>Idio=6</td>
</tr>
<tr>
<td></td>
<td>PP=8</td>
<td>IU=4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarc=2</td>
<td>HM=13</td>
<td></td>
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</table>

Maintenance doses: (A) = prednisolone (mg/day), (B) = cyclosporin A (mg/kg/day), (C) = azathioprine (mg/kg/day)

Uveitic diagnoses include: RV = retinal vasculitis; MFC = multifocal choroiditis; PP = pars planitis; IU = intermediate uveitis; Sarc = sarcoidosis; Idio = idiopathic.
antimetabolite cytotoxic agent, has been used with some success in the treatment of EPU as weekly doses either in combination with prednisolone or as part of triple therapy with CsA and prednisolone. Other more powerful cytotoxic immunosuppressants include the alkylating agents—for example, cyclophosphamide and chlorambucil. Cyclophosphamide is generally restricted to cases of severe refractory uveitis or cases where there are signs of ANCA positive systemic vasculitis with deteriorating organ function. Chlorambucil is rarely used in the UK for the treatment of EPU, and its effectiveness has been questioned. Newer agents which have been used in the treatment of EPU, although not universally, include bromocriptine. Bromocriptine augments the effect of CsA therapy, their synergistic immunosuppressive action being mediated by blockade of prolactin receptors on T cells and thereby inhibiting proliferation.

Figure 2 presents the response to treatment in patients with severe EPU before and after triple therapy with azathioprine (1–3 mg/kg/day), CsA (<5 mg/kg/day), and prednisolone. These patients represent those who ‘failed’ therapy with prednisolone alone or with prednisolone and CsA—that is, those below the line in Figures 1 and 2. Pretreatment visual acuity was generally poor in these patients with 18/24 eyes having 6/12 or worse vision. Triple therapy controlled the inflammation in 14/24 affected eyes, and maintained vision in 10/24 with improvement in vision in 4/24 eyes. It can be seen, therefore, that over 50% of such patients can be rescued from inexorable visual loss by using triple therapy. There still remains a small group who failed with this therapy.

**Treatment guidelines**

It will be clear from the above that a simple general guideline or protocol for the treatment of sight threatening EPU is possible, given our understanding of the mechanism of the disease and how the drugs act. Such a protocol is detailed below and has evolved from our experience in the treatment of over 500 patients with EPU. Before embarking on the protocol, however, a number of investigations are necessary. Investigations in patients with EPU are performed for two reasons: (i) to determine the nature, cause, and severity of the disease, and (ii) to ensure that the patient is generally well enough to tolerate the immunosuppressive drug regimens. A guide to baseline investigations is detailed in Table 2.

If there are no clinical or laboratory based contraindications or relative contraindications to immunosuppression (for example, uncontrolled diabetes for steroid use and poor renal function for CsA therapy), and immunosuppressive therapy is indicated on clinical grounds the following protocol for the induction of immunosuppression has been found to be effective.

1. The acute/active stage of disease is controlled with systemic steroids as primary therapy.

   The first aim is to treat ‘sight threatening’ disease as soon as possible. This is best achieved using systemic corticosteroids at a dose of 0.5–1.0 mg/kg/day. The dose depends on severity and occasionally intravenous pulsed methylprednisolone (1 g/day for 3 days) may be required in order to gain control.

2. Long term control is achieved with low dose CsA therapy as primary therapy, with or without combined low dose steroid therapy.

   The second aim of therapy is to maintain control using additional immunosuppressants. Effective control can be achieved with CsA at a dose of 5 mg/kg/day. However, at this dose maximal effect is not achieved for 7–14 days and it is important therefore to continue an adequate steroid dose during this initial phase. Patients with mild disease (for definition see above) may be controlled on steroids alone if the maintenance dose is less than 10 mg/day. However, monotherapy with low dose CsA can also adequately control mild disease.

   Once effective control has been achieved (usually between 3–6 weeks after commencing therapy) the aim is to control inflammation on a minimally effective dose. Normally, this is achieved by tapering corticosteroids to a
Corticosteroids

Objective assessment of visual acuity

- This is achieved by:
  - Subjective and objective assessment of visual acuity and/or visual field.
  - Objective assessment of the level of inflammation using a standardised scoring system.

Monitoring therapy: endeavouring to secure a successful outcome

- During the induction and maintenance periods of immunosuppressive therapy, close attention to ‘outcomes’ will ensure that control is not lost while attempting to achieve the lowest effective dose.

MONITORING THE THERAPEUTIC RESPONSE

This is achieved by:

- Subjective and objective assessment of visual acuity and/or visual field.
- Objective assessment of the level of inflammation using a standardised scoring system.

Patients should be first reassessed 2 weeks after induction of immunosuppression and thereafter at 4 week intervals until stability is achieved. After a period of at least 3 recurrence free months have passed, immunosuppressive therapy may be tapered further, to the point of treatment cessation if no relapses occur. It is important to emphasise, however, that each patient must have a customised approach depending on their response to treatment.

MINIMISING SIDE EFFECTS

Corticosteroids

- As Figure 1 shows we and others have had success with steroid therapy alone, where after an initial high dose regimen of prednisolone (1 mg/kg/day) the steroid dose is reduced to a maintenance level of <10 mg/day over 3 months. Steroid induced side effects are, however, common if not the rule, and thus are not recommended for long term use at doses over 5–10 mg daily.

- Side effects include a subclinical hypothalamic-pituitary-adrenal axis dysregulation, weight gain, myopathy, abnormal glucose tolerance or diabetes, hypertension, accelerated arteriosclerosis, and atheroma. Weight gain, change in facial appearance, and acne are particularly disturbing to young people. Steroid induced osteoporosis leads to vertebral collapse and an increased incidence of fractures and avascular necrosis. These side effects are cumulative with prolonged therapy. The American Council of Rheumatologists (ACR) reports that long term use of prednisolone at doses greater than 7.5 mg/day can cause significant bone loss and that most patients have low bone mineral density accounting for 25% of fractures in groups of patients. The ACR recommends that those patients who are at high risk should be counselled and appropriate prophylaxis considered and instituted. Mild to severe psychoses are also very common and are significant reasons for reluctance in restarting steroids when relapses occur. Patients who have stopped steroid therapy frequently announce their relief at their freedom from symptoms.

Cyclosporin A

- There is also a concern in ophthalmic practice about the side effects of CsA therapy which has restricted its use, despite its well documented clinical benefit and efficacy in the treatment of EPU. CsA induced nephrotoxicity is dose dependent and may occur even at low doses. Nearly all the patients who commence CsA therapy show biochemical evidence of a proximal tubulopathy which is reversible on dose reduction. The glomerular filtration rate may also be reduced with long term therapy, and not always associated with a rise in serum creatinine. The risk of nephrotoxicity is increased with pre-existing hypertension and with the use of certain drugs such as non-steroidal anti-inflammatory drugs (NSAIDs). Importantly, in one study no significant nephrotoxicity or hypertension was found in young patients (under 30 years) who had systemic associated disease. Hepatotoxicity is an unusual complication in Europe and in our experience rarely raises liver enzymes to necessitate cessation of CsA.

Table 3 Monitoring of immunosuppressant therapy in endogenous posterior uveitis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Monitoring Parameters</th>
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<tbody>
<tr>
<td>Corticosteroids</td>
<td>- Weight, general habitus including skin changes</td>
</tr>
<tr>
<td>- Urinary and random blood glucose (fasting blood glucose and/or glucose tolerance test if indicated)</td>
<td></td>
</tr>
<tr>
<td>- Blood pressure</td>
<td></td>
</tr>
<tr>
<td>- Electrolytes (hypokalaemia)</td>
<td></td>
</tr>
<tr>
<td>- (Bone densitometry)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>- Blood pressure</td>
</tr>
<tr>
<td>- Creatinine, blood urea nitrogen, and regular glomerular filtration rate assessment for renal toxicity</td>
<td></td>
</tr>
<tr>
<td>- Liver function tests</td>
<td></td>
</tr>
<tr>
<td>- Electrolytes, including magnesium</td>
<td></td>
</tr>
<tr>
<td>- Full blood count (particularly lymphopenia)</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>- Full blood count and differential for leucopenia (in particular neutropenia), Anaemia, thrombocytopenia, and leucoerythroblastic anaemia occur more rarely</td>
</tr>
</tbody>
</table>

Lifetimetreatment of transplant patients has shown that CsA therapy is associated with a risk of malignancy, particularly lymphomas. However, the risk in using low dose CsA in uveitis is likely to be low, in part because treatment of EPU with CsA is often a short to mid term therapy (< 2 years) and partly because of the lower doses used.

Control of hypertension in steroid-CsA treated EPU patients is best achieved both by conservative measures including weight loss and reduction in alcohol intake, and by reducing the dose of immunosuppressive agents, in particular high dose corticosteroids in the first instance. CsA therapy can still be given safely to controlled hypertensives, provided renal function is regularly monitored. Blood pressure control is best achieved with calcium antagonists because of its renal protective effect when patients are receiving CsA allowing maintenance of renal function without modulating CsA dose.

It is important to inquire at each visit to the clinic using a simple check list whether the patient has any specific symptoms and signs which might indicate side effects. This should be combined with regular laboratory tests specific for the individual drugs. The common features which require attention are detailed in Table 3. Lastly, it is important to recognise when treating these patients that there are many drug interactions which can increase the toxicity of
the immunosuppressant. In addition, one must avoid combining cytotoxic agents which are myelosuppressive.

The next generation of immunosuppressants

While many cases of EPU are adequately controlled on the above regimen, particularly if carefully monitored to achieve the lowest effective dose of drugs in combination, some patients will escape control. Such patients are either refractory to therapy or more commonly develop intolerable side effects. Newer immunotherapeutic approaches are available and are currently under evaluation and should be considered. These include FK 506,55 mycophenolate mofetil,56 and inhibition of the effector immune response with monoclonal antibodies against specific lymphocytes and proinflammatory cytokines.22 25 Hopefully, these will allow safer and more precise control of inflammation in EPU and thus reduce the morbidity for this disease.2 7

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