Which dose of steroids and which cytotoxics for severe lupus?

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Summary

There have been a number of major advances in the treatment of systemic lupus erythematosus and we are now in the era of biologic therapies for this multisystem autoimmune disorder. There has been a greater awareness of the toxicities of the traditional therapies including the recognition that the doses of corticosteroids used in the past have been excessive, resulting in unacceptable toxicities. Other advances have included the development of lower cumulative doses of cyclophosphamide and the widespread acceptance of mycophenolate mofetil for the treatment of lupus nephritis. This review addresses the current management of severe lupus with corticosteroids and cytotoxic agents.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterised by autoantibody production and major organ dysfunction. Patients may have disease relapses that range from mild self-limiting flares to life-threatening multisystem failure requiring critical care. Each disease flare may result in the accumulation of damage both from the disease process and from the therapies administered. Damage accumulation increases the risk of morbidity and premature mortality. Prevention, prompt recognition and management of disease flares are vital in limiting damage accumulation and improving outcome. Clinicians and patients need to work closely together to identify disease flares at an early stage and for patients to seek medical attention immediately. Expert patients may be able to self-manage mild flares and clinicians should have systems in place to respond rapidly to patients experiencing serious flares. Management should be tailored to the individual patient and is dependent on thorough clinical evaluation and appropriate investigations and stratifying patients into mild, moderate and severe disease categories.

4The authors contributed equally to the manuscript.
Corticosteroids

Since the first use of corticosteroids in rheumatoid arthritis by Philip Hench in 1948, these agents have become the standard of care for moderate to severe inflammatory rheumatic diseases. Immediately after the first patients received corticosteroids however, it became apparent that there were wide ranging adverse effects that have tempered their use. There is now a ground swell of opinion that the doses of corticosteroids used, especially in clinical trial protocols, are excessive [1]. Indeed, the protocolised use of high doses of corticosteroids has been a major confounder in randomised controlled trials of biologic agents in SLE that has led to failure of many of these agents to meet the trial endpoint of superiority or non-inferiority over standard of care therapies.

Glucocorticosteroids are prescribed in conjunction with immunosuppressants to manage severe clinical manifestations of SLE. Depending on the clinical indication, corticosteroids may be administered intravenously (IV), intra-muscularly (IM), intra-articularly (IA) or orally (PO) and have an anti-inflammatory and immunosuppressant mode of action. Methylprednisolone IV 500–1000 mg over 1 hour once a day for 3 days followed by oral prednisolone 0.5–1 mg/kg/day (maximum 60 mg a day) for at least 4 weeks is often prescribed for severe organ-involved systemic lupus erythematosus, such as lupus nephritis. Intra-muscular or intra-articular corticosteroids may be beneficial in managing severe inflammatory arthritis secondary to active lupus. Depot preparations are traditionally used in doses of 80–120 mg methylprednisolone intramuscularly as a single injection and repeated as needed according to clinical response. Intra-articular corticosteroids into large joints may be used in doses of 40–80 mg of methylprednisolone. Other preparations for intra-articular injection include hydrocortisone, triamcinolone and dexamethasone and doses are variable. Oral prednisolone at traditional doses of 0.5–1 mg/kg/day (maximum 60 mg a day) may be prescribed for induction of clinical remission. These doses, however, are not evidence-based and it is likely that much lower doses could be used with similar efficacy and future controlled studies should address this [1]. Although corticosteroids play an important role in the management of severe SLE, they are associated with numerous side-effects including immunosuppression, glucose intolerance, bruising, delayed wound healing, skin thinning, weight gain, insomnia, mood disorders, psychosis, gastrointestinal perforation and an increased cardiovascular risk. The consensus is that the lowest corticosteroid dose necessary to control disease with concomitant immunosuppressant medication should be prescribed whenever possible. It should be noted that prolonged use of high dose corticosteroids impairs the pituitary-adrenal axis therefore corticosteroids should not be stopped abruptly, but rather reduced slowly to avoid an adrenal crisis.

Steroid tapering regimens are variable between clinicians and indeed across geographical regions. For example, in the USA most clinicians aim to taper and stop corticosteroids within 6 months even in patients with moderately severe disease while continuing immunosuppressive therapies. In contrast, in Europe, there is a tendency to continue small doses of prednisolone at 5 mg or 7.5 mg daily as long term maintenance alongside other standard of care therapies.

Cytotoxic treatment

Cytotoxic drugs have been used off-license in the management of SLE for over 50 years, based on clinical experience and expert opinion. The indications for the use of cytotoxic drugs in SLE include neuropsychiatric lupus, inflammatory arthritis, myositis, cutaneous lupus, severe cytopenia, lupus nephritis, vasculitis, pericarditis, myocarditis, interstitial lung disease and pulmonary haemorrhage.

Severe neuropsychiatric lupus

Severe neuropsychiatric lupus may occur as a result of neurotoxic, inflammatory or thrombo-embolic processes. The approach to the management of neuropsychiatric lupus depends on the underlying aetiology. Clinical manifestations such as cerebral vasculitis, aseptic meningitis, aseptic encephalitis, optic neuritis, transverse myelitis, sensori-motor peripheral neuropathy, refractory seizures, acute confusional state and psychosis are often driven by inflammation and may be managed with corticosteroid therapy in combination with immunosuppressant drugs, in addition to all necessary therapeutic interventions targeted at symptom control [2].

Induction therapy

EULAR recommendations for the management of neuropsychiatric lupus were published in 2010 and are based on the systematic review of over 1000 publications of clinical studies and expert opinions [2]. Cyclophosphamide (CYC) is an alkylating agent prescribed for induction therapy in neuropsychiatric lupus and is prescribed in combination with intravenous methylprednisolone and oral prednisolone 0.5–1 mg/kg/day (maximum 60 mg a day) [3,4]. Clinical case reports, case series and one non-randomised clinical trial have reported benefit of intravenous cyclophosphamide for the treatment of a broad spectrum of neuropsychiatric lupus manifestations using a dosing regimen of 500 to 1000 mg/m² monthly for up to 12 months [3,5–12]. In the clinical trial, patients with seizures, optic neuritis, peripheral or cranial neuropathy, coma, brainstem disease, or transverse myelitis were treated with induction methylprednisolone IV 3 g followed by either IV monthly CYC versus IV methylprednisolone bimonthly every 4 months for 1 year and then IV CYC or IV methylprednisolone every 3 months for another year. The cyclophosphamide treated patients achieved 75% clinical improvement compared to methylprednisolone treated patients who achieved 30% clinical improvement.
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A low-dose cyclophosphamide regime of CYC IV 500 mg fortnightly for 3 months followed by a maintenance cytotoxic drug, may be preferable to high dose IV CYC because it reduces the incidence of adverse events related to CYC therapy [13,14].

Oral cyclophosphamide 1–2 mg/kg/day for 6 months followed by maintenance immunosuppression with azathioprine in severe lupus psychosis has been reported to be beneficial in an open label study [15]. However, oral cyclophosphamide is very rarely used especially in young women who may be at risk of ovarian failure.

**Maintenance therapy**

Azathioprine (AZA) antagonises purine metabolism and inhibits the synthesis of DNA, RNA, and proteins thereby reducing immune cell proliferation. Azathioprine PO 2 mg/kg/day is recommended in neuropsychiatric lupus as a steroid-sparing, cyclophosphamide-sparing immunosuppressant [15].

Mycophenolate mofetil (MMF) inhibits the de novo guanosine nucleotide synthesis, impairs the function of T and B lymphocytes and is anti-inflammatory. MMF has been used successfully in the management of inflammatory neuropsychiatric lupus, such as acute transverse myelitis in which complete clinical recovery may be achieved and MRI abnormalities may resolve after treatment [16]. Mycophenolate mofetil PO 500 mg-3 g daily maintenance therapy after induction of clinical remission with cyclophosphamide may be prescribed as a steroid-sparing cytotoxic drug when clinically indicated [17,18].

**Severe musculoskeletal lupus**

Severe inflammatory arthritis and severe inflammatory myositis secondary to systemic lupus erythematosus require management with disease modifying anti-rheumatic drugs or cytotoxics.

**Disease modifying anti-rheumatic drugs (DMARDs)**

Methotrexate (MTX) is a dihydrofolate reductase inhibitor which suppresses the immune system and can induce clinical remission from severe musculoskeletal manifestations of lupus, such as inflammatory arthritis [19,20]. MTX is particularly beneficial in lupus arthritis that has not responded adequately to hydroxychloroquine [21]. Case reports, case series, cohort studies and clinical trial evidence support the use of MTX in lupus arthritis and demonstrate an overall reduction in SLE disease activity scores with the management of the inflammatory arthritis [22]. MTX doses range from 7.5 to 25 mg/week orally or subcutaneously and should be prescribed in conjunction with folic acid PO 5 mg/week or twice weekly to minimise the potential bone marrow suppression side effect of methotrexate. The Toronto Lupus Cohort of patients with severe antimalarial resistant lupus inflammatory arthritis, were studied and over an average period of 3.5 years it was determined that low-dose methotrexate is effective and well tolerated [21].

Leflunomide (LEF) is a pyrimidine synthesis inhibitor which inhibits the proliferation of activated and autoimmune lymphocytes and has an anti-inflammatory effect in SLE patients. Leflunomide may be prescribed for the management of severe inflammatory arthritis as LEF PO 100 mg/day loading dose for 3 days followed by LEF PO 10-20 mg/day with regular monitoring for potential severe adverse events or side effects related to leflunomide therapy[23,24]. Many clinicians however do not use the loading dose in order to minimise adverse events. In an open label study of leflunomide for inflammatory arthritis, this drug has been shown to be efficacious when patients have been clinically assessed 2–3 months post initiation of treatment [23].

**Cytotoxics**

Cyclophosphamide (CYC) IV 750 to 1000 mg/m² monthly for up to 6 months or CYC IV 500 mg fortnightly for 3 months or rarely CYC PO 1-2 mg/kg/day may be prescribed as induction therapy for severe lupus-related inflammatory myositis which has not responded to corticosteroids or other immunosuppressant drugs. However the published evidence for this intervention is limited to case series and reports which mainly report data pertaining to autoimmune inflammatory polymyositis, dermatomyositis and inclusion body myositis – the latter being poorly responsive to any therapies [25,26].

Mycophenolate mofetil PO 500 mg–3 g daily may be prescribed for induction and maintenance therapy for severe inflammatory myositis in SLE patients previously unresponsive to conventional immunosuppressant drugs [27]. MMF has been reported to improve muscle strength and reduce the corticosteroid requirements in inflammatory polymyositis, however there is no randomised clinical trial data for MMF treatment specifically targeted at lupus myositis [26,28].

Azathioprine PO 2 mg/kg/day may be prescribed as a second-line drug for severe inflammatory myositis based on small case series and non-randomised clinical study data that report mild effectiveness in autoimmune inflammatory polymyositis [26].

**Severe cutaneous lupus**

Severe cutaneous lupus may manifest as acute, sub-acute lupus erythematosus, chronic lesions, discoid lupus erythematosus, lupus profundus, lupus panniculitis and lupus cutaneous vasculitis. Corticosteroid therapy in conjunction with cytotoxic disease modifying immunosuppressant drugs may be prescribed when topical treatments and antimalarials such as hydroxychloroquine or mepacrine have failed to control the disease. In general, fixed or scarred lesions including discoid lupus respond poorly to immunosuppressant drugs.
**Methotrexate**

Methotrexate may be prescribed for severe cutaneous lupus, refractory sub-acute cutaneous lupus erythematosus and discoid lupus erythematosus. Randomised controlled trials and case series have shown the effectiveness of methotrexate in managing severe cutaneous lupus at doses ranging from MTX 10–25 mg/week [29–32]. A 6 month randomised placebo controlled double blind trial of methotrexate in severe cutaneous lupus reported a significant reduction in active skin lesions and overall clinical effectiveness, as measured by improvement in SLEDAI [19]. Clinical improvement of skin lesions is rapid with methotrexate and may be noticeable within the first 2 weeks of therapy, with a high incidence of clearance of skin lesions within 3 months of treatment [31].

**Azathioprine**

Azathioprine may be beneficial in both discoid lupus erythematosus and sub-acute cutaneous lupus erythematosus when prescribed at a dose ranging from AZA 100–150 mg/day [33–35]. Cutaneous improvement is usually noticeable within 2 months of treatment.

**Mycophenolate mofetil**

The evidence supporting the management of severe cutaneous and discoid lupus erythematosus with mycophenolate mofetil is based on open label placebo-controlled trials, case series and case reports, which recommend an average dose of MMF 1–3 g per day [36–39]. Clinical response may take approximately 3 months to become evident.

**Thalidomide**

Thalidomide may be useful in the management of severe refractory cutaneous and discoid lupus erythematosus in patients who have been counselled about the potential adverse effects, which include severe peripheral neuropathy and teratogenicity. The dose of thalidomide may initially range between 50–100 mg/day, and it is recommended to use the lowest possible effective dose with close monitoring for adverse events in specialist clinics [40]. Our experience is that SLE patients have an unexpectedly high risk of thalidomide related neurotoxicity and as a result, this therapy is generally only used as a last resort [41].

**Cyclophosphamide**

Cyclophosphamide is rarely prescribed solely for the management of severe cutaneous lupus, and clinical remission from severe cutaneous or discoid lupus erythematosus may be an additional benefit in patients who require cyclophosphamide for systemic manifestations of SLE.

**Cyclosporin A**

There is evidence to suggest that discoid lupus erythematosus may be exacerbated in patients treated with cyclosporin A [42,43]. The few case reports of patients whose refractory cutaneous lupus was treated with cyclosporin A have not shown clinical effectiveness [44,45]. Severe sub-acute cutaneous lupus erythematosus may benefit from hydroxychloroquine and cyclosporin A combination therapy [46].

**Severe haematological manifestations of lupus**

Immune-mediated cytopenias in SLE include severe thrombocytopenia, severe leucopenia and haemolytic anaemia. Corticosteroids and cytotoxic drugs may be prescribed to manage the haematological manifestations of active SLE. Azathioprine (AZA) PO 2 mg/kg/day (maximum dose 150 mg) may be prescribed for autoimmune haemolytic anaemia and severe autoimmune thrombocytopenia as a steroid-sparing agent [47]. Cyclosporin A PO 2.5 mg/kg/day (maximum dose 100 mg bd) may be prescribed for severe autoimmune thrombocytopenia with close monitoring of blood pressure and renal function, since severe hypertension and renal impairment are common side effects of cyclosporin A [48–51].

Cyclophosphamide (CYC) IV 0.75–1.0 g/m² body surface area every month or 500 mg every fortnight for 3 months may be prescribed for the treatment of severe autoimmune thrombocytopenia refractory to standard treatment [52]. Intravenous cyclophosphamide has also been beneficial in lupus-associated aplastic anaemia [53].

Mycophenolate mofetil (MMF) PO 1–3 g/day may be prescribed for the management of severe refractory lupus related thrombocytopenia, leucopaenia, haemolytic anaemia, pure red cell aplasia and aplastic anaemia [54].

**Lupus nephritis**

Lupus nephritis affects approximately 50% of SLE patients and is associated with significant morbidity and mortality [55–57]. Therefore, optimal management of lupus nephritis in both the induction and maintenance phases of therapy is of the utmost importance.

**Induction therapy**

The main treatment choices for the induction phase in lupus nephritis are MMF or CYC with concurrent glucocorticosteroid therapy [58–60]. MMF and CYC are considered equivalent based on clinical studies and expert opinion however patients of different ethnicities may respond differently to therapy. MMF has been shown to have similar efficacy in all races studied to date (Caucasian, Asian, African, Hispanic) [58–60]. There is evidence that African and Hispanic lupus nephritis patients respond less well to intravenous CYC than Caucasian or Asian patients and thus MMF may be a more preferable choice for induction therapy in such individuals [58,61,62].

The optimal dose of MMF varies as per the clinical scenario. The recent American College of Rheumatology (ACR) guidelines for the treatment of lupus nephritis suggest that, for patients with class III/IV nephritis without crescents, both 2 and 3 g total daily
which dose of steroids and which cytotoxics for severe lupus?

Maintenance therapy

The main choices for maintenance therapy in lupus nephritis are AZA or MMF, which have been shown to have similar efficacy in a number of clinical trials. Contreras et al. compared high-dose intravenous CYC, AZA, and MMF as maintenance therapy after induction with monthly intravenous CYC [64]. Mortality rates particularly due to infection were significantly higher in the CYC group as compared with either AZA or MMF. Two other randomized trials, the maintenance phase of the ALMS trial and the MAINTAIN Nephritis Trial, have directly compared AZA and MMF maintenance therapy in lupus nephritis [67].

In the ALMS trial, patients who had responded to MMF or CYC at 6 months were randomly assigned to receive either AZA or MMF for an additional 3 years. The primary outcome measure was time to treatment failure, a composite endpoint comprised of renal flare, doubling of serum creatinine, initiation of rescue therapy, end-stage renal failure, and death. Time to treatment failure was statistically shorter for AZA patients in comparison with those who received MMF [70].

In the MAINTAIN Nephritis Trial, all patients received the Euro-Lupus CYC induction regimen and at 3 months were switched either to AZA or MMF irrespective of their renal response. Time to renal flare did not significantly differ after a 5-year follow-up period with renal flare rates of 19% and 25% for MMF and AZA, respectively [67]. Therefore, two immunosuppressive therapies have been found to be safe and efficacious in the maintenance phase of lupus nephritis. As part of the decision making process of which maintenance therapy to use, one must consider the patients' potential future desire to become pregnant given the known teratogenicity of MMF [71]. The optimal duration of therapy with maintenance AZA or MMF before tapering or withdrawal is as yet unknown and is currently based on the treating physicians' own discretion.

Resistant lupus nephritis

In lupus nephritis patients who fail to clinically respond to induction therapy after 6 months of MMF or intravenous CYC, the ACR guidelines recommend switching the immunosuppressive agent from either CYC to MMF, or from MMF to CYC, accompanied by 3 days of pulse glucocorticosteroid [63]. Should the patient remain resistant to treatment, further immunosuppressive options are available. Open-label trials have shown that lupus nephritis may respond to B-cell depletion therapy in the form of rituximab [72,73]. However, a prospective randomized controlled trial of rituximab versus placebo on a background of MMF and glucocorticosteroids failed to meet its primary end-points [74].

The anti-BlyS/BAFF agent belimumab has been recently approved by the FDA for treatment of SLE. The BLISS-52 and BLISS-76 studies have shown belimumab to be safe and effective in the treatment of seropositive SLE; however, these studies did not include renal or central nervous system lupus [75,76]. Although these studies were not designed to evaluate the response of lupus nephritis to belimumab, 14–18% of patients enrolled had proteinuria of >2 g/24 hours at baseline. In a post-hoc analysis, trends were seen towards a reduction in proteinuria and renal flares in those treated with belimumab 10 mg/kg [77,78].

Severe gastrointestinal lupus

Gastrointestinal symptoms are common in SLE patients and are usually mild, however more severe manifestations can occur namely lupus peritonitis, lupus enteritis, protein-losing enteropathy, and pancreatitis [79]. Given the relative rarity of severe gastrointestinal lupus, there is a paucity of randomised controlled trials of the use of cytotoxic agents. Ascites in an SLE patient may be due to lupus peritonitis or associated disorders, such as pancreatitis, nephrotic syndrome, heart failure, or infection. The majority of publications pertaining to lupus peritonitis are case reports or small case series and their response to corticosteroid therapy [80,81].

Induction therapy

In a study of 69 episodes of SLE-related serositis in Chinese patients, 21 episodes (30%) were peritonitis/ascites. Nonsteroidal anti-inflammatory drugs (NSAIDs) were used in 35% of these cases and moderate to high doses of oral prednisolone were used in 76% [81]. Garrido et al. have published a case demonstrating the efficacy of rituximab combined with
cyclophosphamide in an SLE patient with peritoneal vasculitis refractory to conventional immunosuppressive therapy [82]. Lupus enteritis is a rare and poorly understood cause of abdominal pain in SLE patients although it appears to be more common in South East Asian patients. Clinical symptoms included abdominal pain, vomiting, diarrhoea and fever. The disease may evolve to intestinal necrosis and perforation if untreated [83,84]. In a French cohort of SLE patients with lupus enteritis, all patients received corticosteroids as a first-line therapy, with additional immunosuppression administered either from the initial episode or in case of relapse [83]. Mycophenolate mofetil has been shown to be effective in inducing remission of lupus enteritis [84,85]. Tan et al. published a case of lupus enteritis which resolved following pulse intravenous methylprednisolone and CYC [86]. A resistant case published by Petri et al. described a lupus enteritis patient unresponsive to high-dose corticosteroid, MMF, hydroxychloroquine, and oral CYC. The patient eventually responded when treated with the Euro-Lupus intravenous CYC regimen [84].

Protein-losing enteropathy (PLE), characterized by diarrhoea, oedema, and hypoalbuminaemia, can be the initial presentation of SLE [87–90]. Law et al. reported a series of 48 SLE patients with PLE and their clinical characteristics. Thirty (62.5%) patients responded initially well to a combination of prednisolone and AZA and 33 (68.8%) patients were successfully maintained by this medication combination [87]. In a systematic review by Al-Mogairen of 112 PLE patients all were commenced on corticosteroids, 34% responded to corticosteroids alone, 66% required further immunosuppressive therapy, which included CYC (46%), AZA (33%), and a combination of CYC and AZA (7%) [90]. A few reported cases responded to either cyclosporine or etanercept. Overall prognosis was very good with corticosteroids combined with immunosuppressive therapy.

Lupus pancreatitis is a rare but potentially life-threatening manifestation of SLE, which occurs in 2–4% of lupus patients [91,92]. Given the frequency of corticosteroid use in SLE treatment, the question often arises as to whether corticosteroid use is the aetiological agent in acute pancreatitis in SLE patients, or whether it is related to the underlying disease itself. Derk et al. examined lupus activity and medication history in 25 SLE patients with acute pancreatitis and concluded that corticosteroids did not appear to be the aetiological agent [93]. In a further study by Breuer et al. most cases of lupus pancreatitis were unrelated to treatment with corticosteroids or azathioprine [94]. Yang et al. published a case series of 27 patients with lupus pancreatitis, of whom 16 received intensive glucocorticoid treatment and 75% exhibited favourable prognosis [95]. Ben Dhaou et al. reported a series of six lupus pancreatitis patients, all treated by high doses of glucocorticoids. The outcome was favourable in five patients, and one patient died [96]. There are a limited number of publications in the literature as to use of cytotoxic agents in lupus pancreatitis. Rituximab has been reported to be effective in the treatment of lupus pancreatitis [97].

**Severe cardiovascular and respiratory lupus**

There are a number of possible cardiac manifestations of SLE, the most common forms being pericarditis, myocarditis, non-bacterial endocarditis, premature coronary atherosclerosis, congestive heart failure, cardiac arrhythmias and pulmonary hypertension.

**Cardiovascular lupus: induction therapy**

On review of the literature, the most commonly used immunosuppressive treatment for acute flares is high-dose corticosteroids followed by pulse CYC [98,99]. After treatment of the acute phase, there is no general consensus as to optimal long-term therapy of severe cardiovascular lupus.

**Respiratory lupus: induction therapy**

Respiratory involvement in SLE most commonly manifests as lupus pleuritis [100]. Less frequently seen but potentially more severe pulmonary complications include acute lupus pneumonitis, chronic interstitial lung disease, diffuse alveolar haemorrhage and shrinking lung syndrome [101–103]. Unsurprisingly given the relative rarity of severe respiratory lupus no large randomised controlled trials exist.

A number of small case series exist describing the use of CYC and corticosteroids in diffuse alveolar haemorrhage in lupus nephritis patients [104,105]. In addition, there are published case reports of successful treatment of lupus pneumonitis and shrinking lung syndrome with rituximab [106–108]. The BLISS-52 and BLISS-76 randomised controlled trials both enrolled a small proportion of patients with severe cardiovascular and respiratory lupus. Both trials showed a positive clinical response to therapy with belimumab and the FDA has since approved the drug for use in seropositive SLE patients without severe nephritis or central nervous system disease [75,76].

A randomised controlled trial of the CTLA4-Ig fusion protein, abatacept which causes blockade of co-stimulatory interaction of T and B lymphocytes has been undertaken in 175 SLE patients with polyarthritis, discoid lesions, pleuritis and/or pericarditis. The study failed to meet its primary end-point of a reduction of the proportion of patients with a new SLE flare. There was however some improvement in quality of life measures by the SF-36 physical component scores in those treated with abatacept [109].

**Summary**

SLE is a complex systemic autoimmune disease whose prognosis has improved significantly over the last three decades. Treatment regimens have been developed through expert opinion, case series and cohort studies and more recently
with large scale randomised controlled trials. The use of corticosteroids and immunosuppressive agents has been refined over the last few years and clinicians generally attempt to tailor treatment to the individual patient’s manifestations. The use of biologic agents will increase over the next decade and, combined with minimization of corticosteroid induced damage, the outlook for patients should continue to improve.

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References


[54]之下引用のための文献をリストアップ

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