Systemic lupus erythematosus: treatment

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LEARNING OBJECTIVES

- Select the best treatment for patients with simple and complex manifestations of systemic lupus erythematosus (SLE) including lupus nephritis (LN)
- Support your treatment decisions on the basis of evidence
- Appreciate the risks and side-effect profiles of commonly used medications for SLE
- Critically manage the risk factors for cardiovascular disease and other comorbidities
- Evaluate which drugs can be used during pregnancy and how to treat active SLE during pregnancy
Treatment of systemic lupus erythematosus (SLE) has several goals: (i) induction of a prompt response, aimed at controlling disease activity; (ii) maintenance therapy, aimed at maintaining the response and at preventing flares; and (iii) prevention and treatment of comorbidities (e.g., hypertension, diabetes mellitus, osteoporosis) and of drug-induced damage. The armamentarium of therapies for SLE include glucocorticoids, antimalarials, conventional synthetic immunosuppressive drugs as well as biologic therapies. During the last two decades, major improvements in the treatment of SLE can be mainly attributed to a better use of traditional immunosuppressive drugs. Although an array of new biological drugs has been developed and tested in the last decades and more are underway, only one new drug, belimumab, has been approved for the treatment of SLE.

The first part of this chapter is dedicated to review the scientific evidence for the use of different drugs; in the second part, we propose therapeutic protocols dealing with specific organ involvement; finally, comorbidities and non-adherence will be discussed. Specific treatment for the antiphospholipid syndrome is described in another chapter.

The reader is strongly encouraged to read the EULAR, EULAR/ERA-EDTA and ACR recommendations for the treatment of lupus and lupus nephritis (LN) (Bertsias, 2008; Bertsias, 2012; Hahn, 2012), and to integrate a treat-to-target approach in her/his daily practice (Mosca, 2012; van Vollenhoven, 2014).

1. THERAPEUTIC AGENTS

1.1 Glucocorticoids

Glucocorticoids (GCs) are the mainstay of treatment of SLE as induction therapy and to manage acute flares and have dramatically improved the prognosis of severe SLE. Thus, survival rates have increased from 50% at 3 years in the 1950s (Jessar, 1953) to 92% at 10 years in recent series (Cervera, 2003). GC regimens vary from low dose (0.1-0.2 mg prednisone/kg/day or equivalent) to moderate (0.2-0.5 mg/kg/day) or high (0.5-1 mg/kg/day) dose, according to the type of organ involvement, as discussed below. Of note, these dosages of GCs based on body weight and especially the high dose of 1mg/kg/day are not evidence-based. As much as the use of GCs has improved the outlook of SLE, limiting their use is of equal importance, since evidence is accumulating that GCs might contribute to irreversible damage (Al Sawah, 2015). Interestingly, the initial dose of prednisone in the first month of treatment is predictive of the prednisone doses over the following 11 months (Ruiz-Irastorza, 2016).

Intravenous (IV) pulse methylprednisolone therapy, mostly 500-1,000 mg daily for 1-3 days, was introduced in the 1970s (Cathcart, 1976) and is remarkably efficacious in critically ill patients (Isenberg, 1982), suffering renal impairment, central nervous system disease, severe arthritis, pleuroperticarditis or thrombopenia, although the
jury is still out regarding the dose of IV methylprednisolone needed to achieve rapid control of activity (Franchin, 2006).

Tapering schedules are mainly based on physician’s experience and clinical judgment. In the National Institute of Health (NIH) protocol for the treatment of lupus nephritis (LN), after three IV methylprednisolone pulses (1,000 mg/day for three days), patients were given oral prednisone 0.5 mg/kg/day for 4 weeks and the dose was further tapered by 5 mg every other day each week to a dose of 0.25 mg/kg every other day or the minimal dose required to control extra-renal disease (Austin, 1986; Boumpas, 1992; Gourley, 1996; Steinberg, 1991). In the Euro-Lupus Nephritis Trial, after three consecutive IV methylprednisolone daily pulses of 750 mg, patients were switched to oral prednisolone (mostly 0.5 mg/kg/day for 1 month; 1 mg/kg/day in severe cases) which was tapered by 2.5 mg/day every 2 weeks to reach a maintenance dose of 5-7.5 mg/day at 4-6 months (Houssiau, 2002). In a recent series of LN patients, induction therapy without oral steroids was given consisting of 2 pulses of IV methylprednisolone 500mg and 2 doses of 1 gram of rituximab given 2 weeks apart followed by mycophenolate mofetil. Although pioneering, this was not a randomized controlled trial and patients represented a population without much extra renal disease (Condon, 2013).

Many SLE patients are maintained for years on low dose GCs (between 2.5 and 7.5 mg prednisolone/day) (Badsha, 2002). Chronic use of high dose GCs is associated with increased risk of infection and metabolic (Cushingoid features, diabetes, cardiovascular events), musculoskeletal (myopathy, avascular osteonecrosis, osteoporosis) and other side-effects such as easy bruising and early cataract. Longitudinal cohort studies have confirmed that GCs contribute to damage accrual in SLE, as measured by the SLICC/ACR damage index (DI). The mean DI rose from 0.33 at baseline to 1.9 after 15 years of follow-up in an inception cohort and damage was considered as GC-related in 16% and 49% of the patients at baseline and last follow-up, respectively (Gladman, 2003). In another cohort, the accrual of organ damage was found to correlate with the mean daily prednisone dose, with the risk increasing for doses higher than 6 mg per day (Thamer, 2009). Finally, damage accrual was found to be associated with higher risk of mortality, every one point increase in DI being associated with a 1.32 times higher mortality during follow-up (Chambers, 2009). In these studies the possible confounding effect of disease activity itself should be noted (higher disease activity is associated with both higher dosages of prednisone and damage accrual) and despite statistical modelling remains difficult to completely correct for.

Taken together, while GC remain an inescapable therapy in severe acute SLE cases, many concerns are raised by patients and their physicians regarding their chronic use as maintenance therapy. As a consequence, patients should receive the lowest possible dose of GC for the shortest period of time. In this respect, other immunosuppressants, such as azathioprine or methotrexate can be efficacious GC-sparing agents, although robust data obtained from randomized trials are relatively scarce (Fortin, 2008). Recent data from the Belimumab trials suggest that belimumab can be a steroid-sparing agent in lupus patients, with more patients
who decreased oral GCs and less patients with increases in oral GCs in the belimumab groups (Van Vollenhoven, 2016). In patients requiring GC, adequate prevention of bone loss should be applied, keeping in mind that GC-induced osteoporosis is an early event. Patients must be immunized against influenza (every year) and Streptococcus pneumoniae (every 5 years) (Naveau, 2005).

1.2 Antimalarials

Antimalarials are widely prescribed to SLE patients. Hydroxychloroquine sulphate (HCQ) is the most frequently used, at doses ranging from 200 to 400 mg/day (maximum 6.5 mg/kg ideal body weight/day). Other antimalarials such as chloroquine (125-250 mg/day; maximum 4 mg/kg/day) and quinacrine (100 mg/day) are preferred for severe cutaneous cases (Okon, 2013). HCQ is an alkalinizing lysosomatropic drug that accumulates in lysosomes where it inhibits some important functions by increasing the ph. It can inhibit toll like receptor signalling, the accumulation of nucleic fragments in lysosomes, the autophagic degradation and it can inhibit the binding of beta-2-glycoprotein to phospholipids (Ponticelli, 2017). Of note, tobacco smoking reduces the efficacy of antimalarials (Ezra, 2012).

While mucocutaneous and articular manifestations are the original indications for the use of antimalarials in SLE, pivotal data have shown that these drugs are beneficial in a wider variety of disease manifestations. The Canadian Hydroxychloroquine Study Group placebo-controlled randomized study demonstrated that HCQ withdrawal in clinically stable SLE patients was associated with an increased flare rate (The Canadian Hydroxychloroquine Study, 1991; Tsakonas, 1998). In addition, uncontrolled data from the LUMINA cohort (LUPus in the MInorities, NAture versus nurture) indicated that therapy with HCQ independently reduces damage accrual (Fessler, 2005; Alarcon, 2007), including renal damage (Pons-Estel, 2009). Likewise, observational data from the Grupo Latino Americano de Estudio del Lupus suggested that HCQ improved survival rate (Shinjo, 2010), although critics have mentioned channelling bias as a limitation in these studies.

Besides better lupus disease control, antimalarials display many other interesting properties, such as lipid profile improvement (Tam, 2000), prevention of thrombotic events, influence on cardiovascular risk, and a beneficial effect on bone mineral density (Ruiz-Irastorza, 2006 and 2010; Espinola, 2002). A recent retrospective review of pregnancies in mothers with offspring affected by congenital heart block (CHB) suggests that HCQ use significantly reduces the recurrence of CHB (21.7% in non-HCQ users versus 7.5% in HCQ users) (Izmirly, 2012). Finally, HCQ whole blood measurements was recently found to be a reliable marker of adherence to therapy (Costedoat-Chalumeau, 2013). Conversely, low levels of HCQ suggesting poor adherence have been found to be predictive of flares (Costedoat-Chalumeau, 2007). Therefore, many experts currently advice to prescribe HCQ (minimum 200 mg/day) in all SLE patients, even in the absence of overt clinical manifestations (D’Cruz, 2001).
Antimalarials are considered safe and well tolerated and can be safely used during pregnancy. Side-effects include digestive intolerance (diarrhoea), skin rash, aquagenic pruritus, blue-grey or brown lower leg hyperpigmentation (Jallouli, 2013), cardiomyopathy, myopathy and retinopathy. Retinopathy can present with photophobia, blurred distance vision, missing or blacked out areas in the vision field (or while reading) and light flashes. Retinopathy is rare with HCQ at doses below 6.5mg/kg/day, and somewhat less exceptional with long-term chloroquine use. New data about the prevalence of retinopathy has led to a recent update of the American Guidelines of Ophthalmology for toxicity screening (Marmor, 2016). At the previously recommended doses of 6.5 mg/kg ideal weight/day the risk of retinal toxicity after 5 years is <1%, after 10 years <2%, but it appears to rise to almost 20% after 20 years. However, in patients with HCQ lower than or equal to 5 mg/kg, without signs of toxicity, the risk appeared much lower (Melles, 2014). Therefore, a maximum recommended dose of 5 mg/kg of observed (rather than ideal) body weight is proposed. In addition, a baseline fundoscopy and annual screening starting after 5 years, for patients on acceptable doses without major risk factors, is recommended. For patients on higher dosages or patients with risk factors more frequent examinations are recommended. Risk factors include age over 60 years, pre-existing macular degeneration, retinal dystrophy, obesity, liver disease and renal failure (Marmor, 2002; Mosca, 2009) and should be assessed regularly. Use of tamoxifen has been identified as an additional risk factor (Marmor, 2016). The rheumatology world has not yet adopted these new recommendations and some critical comments have been published.

In summary, antimalarials are safe and effective in treating musculoskeletal and mucocutaneous manifestations of SLE and reducing the risk of flares, and may have additional benefits in reducing organ damage in the long-term, allowing the reduction of GCs, and decreasing the risk for thromboses, atherosclerosis and osteoporosis.

1.3 Cyclophosphamide

Cyclophosphamide (CYC) was first used in SLE in the late 1970s at the Mayo Clinic as an oral drug to treat LN (Donadio, 1978). Sometimes oral CYC is still used for a limited time course (3 months; 1-2 mg/kg/day) as induction therapy (Mok, 2006; Ponticelli, 2010) but because of concerns regarding the side-effects of long-term exposure to oral CYC, such as alopecia, bladder cancer, haemorrhagic cystitis, bone marrow suppression, haematological malignancies, myelodysplasia and premature gonadal failure, most clinicians have moved to IV CYC.

The first IV CYC protocol was developed at the NIH and consisted of 6 monthly pulses of CYC (750-1,000 mg/m2) followed by quarterly pulses (at a similar dose) for 2 additional years, usually in combination with IV methylprednisolone pulse therapy and GCs (Austin, 1986; Boumpas, 1992; Gourley, 1996; Illei 2001). This protocol has been the standard of care for proliferative LN during two decades, as well as for severe non-renal lupus, despite the risk of severe infections linked to drug-induced neutropenia and other risks and side-effects.
The administration of anti-emetic drugs before pulse CYC reduces nausea and vomiting and IV hyper hydration and the use of 2-mercaptoethane sodium sulfonate (Mesna), which binds toxic metabolites, can be used to reduce the incidence of haemorrhagic cystitis. The use of MESNA is not strongly evidence-based, nor is the risk of bladder toxicity associated with IV CYC in rheumatic diseases as compared to the use in oncology, as elaborated in a review (Monach, 2010). The use can be considered on an individual basis, taking into account the dose and duration, oral versus IV CYC, other risk factors and the tolerability to hyper hydration. A major concern with this long-course IV CYC regimen is the risk of premature gonadal failure in female patients of child-bearing age, which is strongly dependent on cumulative dose but also on the age of the patient (Boumpas, 1993; Ioannidis, 2002; Katsifis, 2004). An increased incidence of cervical intraepithelial neoplasia in lupus women treated with high-dose IV CYC has also been reported (Ognenovski, 2004). This explains why a long-course of quarterly IV CYC pulses is not recommended anymore as maintenance therapy of LN (Bertsias, 2012; Hahn, 2012).

In order to reduce side-effects, a lower-dose IV CYC regimen (6 x 500 mg fixed dose every two weeks), followed by azathioprine (after 3 months), was developed at St-Thomas’ Hospital in London (Houssiau, 1991; Haga, 1992) and further compared to a long-course IV CYC regimen in a controlled trial, the Euro-Lupus Nephritis Trial (Houssiau, 2002; Houssiau, 2004; Houssiau, 2010). Based on the positive results of this trial, the so-called “Euro-Lupus regimen” is now an accepted option for the treatment of proliferative LN (Bertsias, 2012; Hahn, 2012). While the original Euro-Lupus study represented mostly Caucasian patients with moderate LN, the Euro-Lupus regimen has also been shown effective in a population of more severe LN patients of more racially diverse background in a US-based study (ACCESS trial) (Wofsy, 2013, 2015). Of note, ethnicity might be of importance for the efficacy of IV CYC. Hispanic and black patients have shown lower response rates to IV CYC (in studies compared to MMF) (Isenberg, 2010). In Asian LN patients, the EURO-Lupus regime was evaluated against MMF without any observed differences (Rathi, 2016).

Finally, very high immunoablativew doses of IV CYC have been tested in refractory lupus cases, with improvement in disease activity (Brodsky, 1998; Petri, 2003; Petri 2006).

1.4 Azathioprine

Azathioprine (AZA) is used in clinical practice as a GC-sparing agent in several autoimmune/inflammatory diseases, including SLE. The drug is transformed to 6-mercaptopurine (6-MP) and then to its active metabolites, thiosinic and thioguanilic acid (6 TGN), which incorporate into DNA, thereby causing DNA/protein crosslinks and interfering with nucleic acid structure. The daily dose of AZA is between 1 and 2.5 mg/kg. Gastrointestinal intolerance is the most common side-effect. Bone marrow suppression, increased risk of infections, hepatitis and hypersensitivity reaction are potentially severe but rare adverse events. Because allopurinol blocks xanthine oxidase (one of the enzymes that metabolizes 6-MP), these two drugs are generally
not combined. If both must be taken, the dose of AZA must be reduced by 50-75% to prevent bone marrow toxicity. In case of co-administration of AZA with warfarin, a higher dose of the anticoagulant may be required to maintain therapeutic INR levels (Ng, 2006).

Individuals who are completely deficient in thiopurine methyltransferase, the main enzyme responsible for metabolism of 6-MP (1/300) can develop severe pancytopenia on AZA. TPMT deficiency is not rare and some authorities recommend genotyping before starting AZA treatment; the drug should not be prescribed in case of homozygous deficiency and the dose should be carefully titrated upwards in case of heterozygous mutations (Payne K, 2007). However, genotyping is not done routinely by many rheumatologists; a frequent approach is to start and titrate therapy in steps from a low dosage (50mg) up to the desired dose and check tolerability and blood count after every increase, for example every two weeks.

AZA use has been best studied in LN, either as induction therapy (Grootscholten, 2006; Grootscholten, 2007) or as maintenance treatment (Houssiau, 2002; Houssiau, 2010b). Furthermore, it is effective as an immunosuppressive and steroid sparing agent in other manifestations of SLE. One of the advantages of AZA is its safety in pregnancy; the drug can be continued in pregnant LN patients who need long-term maintenance therapy, often as an alternative to mycophenolate mofetil (MMF) which must be stopped due to its teratogenicity (Perez-Aytes, 2008).

1.5 Methotrexate

Data on the use of methotrexate (MTX) in SLE derive from small cases series, uncontrolled studies and a few controlled trials (Fortin, 2008). MTX, at doses up to 15–25 mg/week, seems efficacious not only in the treatment of articular manifestations refractory to low-dose steroids and antimalarials, but also in the treatment of serositis, cutaneous manifestations, and other features of moderately severe systemic lupus. A systematic review on 3 RCTs and 6 cohort studies showed that MTX was associated with lower SLEDAI scores when compared to controls and significant reductions in corticosteroid use (Sakthiswary, 2014). Small case series suggest MTX may also work for lupus vasculitis and some haematological manifestations, and in a small number of cases it has been given intrathecal for central nervous system lupus (Winzer, 2010).

The safety profile of MTX in SLE patients is similar compared to rheumatoid arthritis (RA) patients. However, because disease-related renal impairment is more frequent in SLE, MTX dose reduction may be required in LN patients with renal failure. Although MTX is generally well tolerated, it can cause dyspepsia, headache, general malaise, increase in serum liver enzyme levels and bone marrow toxicity, the two latter side-effects requiring regular blood monitoring. Rarely, a dry non-productive cough can be the symptom of MTX-induced interstitial lung disease.
1.6 Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a reversible inhibitor of inosine monophosphate dehydrogenase (IMP-DH) and has lymphocyte-selective cytostatic effects, inhibiting T and B lymphocyte proliferation. The drug, used at a dose between 1 and 3 g/day, was gradually introduced into the therapeutic armamentarium for SLE since the end of the 1990s (Glicklich, 1998; Gaubitz, 1999) and subsequently studied in several large randomized controlled trials (RCTs) in LN. These trials showed that MMF is efficacious as induction (Chan, 2000; Ginzler 2005; Ong, 2005; Appel, 2009) and maintenance therapy (Contreras, 2004; Dooley 2011; Houssiau, 2010b). MMF was further tested in open series of patients suffering from renal or non-renal disease (Karim, 2002; Bijl, 2003; Pisoni 2005). A recent cohort study showed its efficacy in refractory to standard of care non-renal manifestations and reduction of corticosteroid use (Tselios, 2016).

MMF side effects are generally moderate and rarely lead to treatment discontinuation. They mainly consist of gastrointestinal manifestations (diarrhoea, nausea, vomiting), hepatitis and anaemia, the latter mainly observed in patients with renal impairment. Other side effects such as pancreatitis and febrile pancytopenia have been observed rarely. The drug is strictly contraindicated in pregnancy (at least during the first trimester) because of proven teratogenicity, with peculiar involvement of the face (Perez-Aytes, 2008).

Recently, a new drug containing mycophenolic acid, the active metabolite of MMF, became available. One gram of mycophenolate mofetil corresponds to 720 mg of mycophenolate sodium. This new formulation may have better gastrointestinal tolerability (Budde, 2004) and was tested in LN (Zeher, 2011).

1.7 Calcineurin inhibitors

Calcineurin inhibitors (CNI) display two modes of action. First, they inhibit T-cell mediated responses, such as cytokine production (e.g. of IL-2), leading to reduced immune activation and glomerular immune complex deposition. Second, they stabilize the podocyte actin cytoskeleton thereby contributing to maintenance of the integrity of the filtration barrier and explaining their potent antiproteinuric effect in LN patients (Faul, 2008).

Cyclosporine A (CSA) has been used to treat a variety of clinical manifestations, as reviewed elsewhere (Griffiths, 2001; Morton, 2000) but has been best studied in LN, including membranous nephropathy. At an initial dose of 4-5 mg/kg/day, CSA was found as efficacious as IV CYC in a randomized trial performed in patients with proliferative LN (Zavada, 2010). The drug was also compared against AZA for maintenance therapy of LN (Moroni, 2006). It is not always well tolerated: transient increase in serum creatinine, hypertension, hypertrichosis, gum hypertrophy, tremor and seizures may occur (Conti, 2000).

Tacrolimus (TAC) is a macrolide compound isolated from a soil fungus found in Northern Japan and is now widely prescribed in transplantation. It has been tested in proliferative and membranous LN in Asian populations (Mok, 2005; Szeto, 2008; Miyasaka, 2009) and was found to have similar efficacy as MMF in a
randomized trial (Mok, 2016), although a trend towards more renal flares and functional decline was observed in the follow-up. Multi-target therapy, combining TAC, MMF and GC, was shown to induce a higher rate of early renal remission compared to IV CYC (Bao, 2008; Liu, 2015), with a note of caution regarding possible rebound proteinuria when TAC is withdrawn. A positive note is that TAC has no known negative effects on fertility and pregnancy. A new CNI, voclosporine, is currently being tested in LN in combination with MMF.

Current practice is not to use CNI as first therapy in LN due to their potential toxicity. They can be useful in selected cases with persistent proteinuria despite standard immunosuppression.

1.8 Thalidomide

Thalidomide (THA), formerly marketed as Softenon, was developed as an antiemetic drug to relieve morning sickness of pregnant women and as a sleeping pill. In the early 1960s, it was found to be dramatically teratogenic (phocomelia) and was withdrawn. Further studies have shown its efficacy in the treatment of leprosy and multiple myeloma. The mechanism of action of the drug is poorly understood, but it appears to display antiangiogenic effects. THA has been used in SLE since the early 1980s (usually 50 mg/day at night) and many studies have demonstrated its efficacy (Pelle, 2003; Coelho, 2005; Cuadrado, 2005). THA is mostly prescribed for severe chronic discoid lupus resistant to antimalarials, with usually very impressive results. Toxicity is the major limiting factor. Thus, polyneuropathy is frequent (at least 20% of patients), can be disabling and is mostly irreversible (Briani, 2004). Patients on THA require regular neurological assessments and electromyography. In some countries, a monthly negative pregnancy test is required before the drug can be prescribed and obtained. Relapses after discontinuation are frequent and may justify the use of a lower maintenance dose such as 50 mg three times weekly.

Immunomodulatory analogues of THA have been developed, such as pomalidomide and lenalidomide, which are purported to be more potent and less toxic than THA. Lenalidomide was recently studied in refractory cases of cutaneous lupus (Cortes-Hernandes, 2012).

1.9 Dapsone

Dapsone, (DAP), 4,4 – diaminodiphenylsulfone, is used in the treatment of dermatitis herpetiformis and as antimycobacterial drug in leprosy. The efficacy of the drug in SLE was suggested in case reports and small series (Fenton, 1986; Neri, 1999; Chang, 2011). DAP seems efficacious in treating bullous LE, subacute cutaneous lupus and mucosal ulcers. It is suggested to start with 100 mg daily and then to taper to the minimally efficacious dose in 2-3 months. DAP can cause nausea and dyspepsia. Major side effects include haemolysis, especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and polyneuropathy. Methaemoglobinemia is the rule in patients treated with DAP but is not, per se, a reason to withdraw therapy, except if it induces a decrease in haemoglobin.
1.10 Leflunomide

Leflunomide (LEF) is a synthetic isoxazole derivative of low molecular weight, with immunomodulatory and anti-inflammatory effects. Its efficacy in the treatment of rheumatoid arthritis and psoriatic arthritis is well established, and some data have been published on its efficacy in SLE (Remer, 2001; Tam, 2004) and even LN (Tam, 2006). In the absence of proper controlled trial its use should be limited to selected cases. Its pros and cons have been described by Wu, 2013.

1.11 Intravenous immunoglobulin

Intravenous immunoglobulins (IVIG) are used as rescue therapy in many refractory autoimmune diseases and some reports suggest its efficacy as treatment of difficult SLE cases (Sherer, 2006). It may be given at 1-2 g/kg/day for 2 consecutive days or 0.4 g/kg/day for 5 consecutive days, and can be repeated monthly as maintenance therapy. Treatment duration in reported series has varied from a few months to years. Except for a clear role in the treatment of SLE-related thrombocytopenia and/or haemolytic anaemia, no other clinical indications for IVIG are supported by strong evidence. IVIG has been used in the management of critically-ill SLE patients (Engel, 1999), but also as a treatment for mild to moderate SLE, in LN (RCT, Boletis, 1999), and for the prevention of recurrent pregnancy losses. Treatment with IVIG is associated with a small risk for thromboembolism but has otherwise surprisingly few side-effects. In contrast to conventional immunosuppressants, IVIG therapy does not increase the infection risk and may therefore be considered proposed in selected cases when concomitant infection cannot be ruled out. Also, IVIG are safe to use in pregnancy. Treatment cost and lack of evidence-based recommendations clearly limit their use.

1.12 Plasma exchange

Plasma exchange (PE) has an established role in the treatment of several autoimmune diseases and syndromes, such as Goodpasture syndrome and microangiopathic haemolytic anaemia. PE has been used to treat various manifestations of SLE over the past 35 years (Pagnoux, 2005), and case reports have suggested effectiveness in controlling severe disease activity, such as alveolar haemorrhage, catastrophic anti-phospholipid syndrome (Bortolati, 2009), neurological involvement (Bartolucci, 2007), haematological manifestations, pericarditis, myocarditis, nephritis, and vasculitis and severe SLE in pregnant patients with or without the anti-phospholipid syndrome (Zandman, 20015). However, a controlled trial comparing the efficacy of PE as treatment of LN in addition to IV CYC failed to show any benefit (Lewis, 1992). Moreover, in uncontrolled series PE in combination with IV CYC in SLE was associated with more severe infections and deaths compared to IV CYC alone (Aringer, 1998). Therefore, PE should probably only be considered as an adjunctive therapy in conjunction with high dose GCs and IV CYC in severely ill patients with SLE where specific pathophysiological mechanisms are activated, such as microangiopathy or catastrophic anti-phospholipid syndrome.
1.13 Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) is a high-risk procedure involving a conditioning regimen to eliminate autoreactive lymphocytes, followed by infusion of previously harvested autologous haematopoietic stem cells, with the aim of reconstructing the immune system. HSCT is becoming a therapeutic option in severe systemic sclerosis and has been used in severe refractory SLE (Alchi B, 2013). Procedure-related mortality is currently too high to propose HSCT, except within the frame of investigational protocols. Basically, only patients with very severe uncontrolled disease and at risk for permanent organ damage or death should be considered for this procedure.

1.14 Mesenchymal stem cell therapy

Several open studies suggest that allogeneic mesenchymal stem cell (MSC) therapy might be useful as adjunct therapy of lupus or LN (Liang, 2010; Sun, 2009; Sun, 2010). It should be stressed, however, that none of these trials were controlled and that the fate of MSC in vivo and their mechanism of actions are far from unravelled (Tyndall, 2010).

1.15 Targeted therapies

New insights in the pathophysiology of SLE and advances in biotechnology have led to a large number of targeted therapies that have been tested in SLE. So far, only the monoclonal anti-BLyS antibody belimumab has been approved for lupus by the EMA and the FDA. The anti-CD20 monoclonal rituximab has been used as an off-label drug, sometimes with apparent success in individual patients, but failed to demonstrate efficacy in randomized controlled trials. The design and choice of outcome measures in trials for a heterogeneous disease such as lupus is a challenge and may have contributed to negative results in the past. The use of some biologics was associated with a high rate of infectious side effects in SLE, such as the anti-CD20 monoclonal ocrelizumab and the anti-BLyS/APRIL receptor construct atacicept. Many targeted therapies are still under investigation in Phase II/III clinical trials. Table Ia lists the main clinical trials performed with biologics in SLE. Table Ib lists the trials that are still ongoing.
## Table Ia: Targeted therapies in SLE – Trials in bold met their primary endpoint

<table>
<thead>
<tr>
<th>Target</th>
<th>Molecule</th>
<th>Acronym</th>
<th>L/LN</th>
<th>Phase</th>
<th>N</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>CD20</td>
<td>Rituximab</td>
<td>EXPLORER</td>
<td>L</td>
<td>II/III</td>
<td>257</td>
<td>No proven benefit vs SOC</td>
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<tr>
<td></td>
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<td>LUNAR</td>
<td>LN</td>
<td>III</td>
<td>144</td>
<td>11% more responders but not statistically significant</td>
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<td>Rovin, 2012</td>
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<tr>
<td>CD20</td>
<td>Ocrelizumab</td>
<td>BELONG</td>
<td>LN</td>
<td>III</td>
<td>381</td>
<td>Early termination – Infections (combo with MMF)</td>
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<td>Mysler, 2013</td>
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<td>CD22</td>
<td>Epratuzumab</td>
<td>ALLEVIEATE 1/2</td>
<td>L</td>
<td>II</td>
<td>90</td>
<td>Early termination – No drug supply</td>
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<td>Wallace, 2013</td>
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<td></td>
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<td>EMBLEM</td>
<td>L</td>
<td>IIb</td>
<td>227</td>
<td>More BICLA responders</td>
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<td>Wallace, 2014</td>
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<td>EMBOBY 1</td>
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<td>III</td>
<td>786</td>
<td>No benefit vs SOC</td>
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<td>EMBOBY 2</td>
<td>L</td>
<td>III</td>
<td>788</td>
<td>No benefit vs SOC</td>
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<td>More BICLA responders</td>
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<td>Wofsy, 2013a</td>
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<td></td>
<td>L</td>
<td>II</td>
<td>85</td>
<td>Early termination – Thrombosis</td>
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</table>

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L: SLE; LN: lupus nephritis; N: number of patients included; SOC: standard of care; NS: not significant; MMF: mycophenolate mofetil; BICLA: British Isles Combined Lupus Assessment; SRI: Systemic lupus erythematosus Responder Index; IFN: interferon; BILAG: Bursitis Isles Lupus Assessment Group index; GC: glucocorticoids; EL: Euro-Lupus; IV: intravenous; CYC: cyclophosphamide.

### Table Ib: Targeted therapies in SLE – ongoing trials

<table>
<thead>
<tr>
<th>Target</th>
<th>Molecule</th>
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<th>L/LN</th>
<th>Phase</th>
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<td>LN</td>
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<td>RTX + IV MP + MMF vs GC + IV MP + MMF induction (NCT01773616)</td>
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<td>RTX for persistent proteinuria despite 6 months of standard immunosuppression (NCT01673295)</td>
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<td>RTX/BEL</td>
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<td>III</td>
<td>RTX + CYL vs RTX + CYC + BEL safety (NCT02260934)</td>
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<td>EMBRACE</td>
<td>L</td>
<td>III</td>
<td>BEL in SLE black race (NCT01632241)</td>
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<td>BEL + CYC or MMF induction vs placebo. BEL + AZA or MMF maintenance vs placebo (NCT01639339)</td>
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<td>Sc BL in addition to SOC (NCT01395745, NCT02074020)</td>
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<td>ANF + MMF vs placebo + MMF (NCT02446899)</td>
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<td>III</td>
<td>ABA vs placebo on background MMF + GC (NCT01714817)</td>
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</table>

L: SLE; LN: lupus nephritis; SOC: standard of care; RTX: rituximab; IV MP: intravenous methylprednisolone; GC: glucocorticoids oral; MMF: mycophenolate mofetil; BEL: belimumab; BL: blisibimod; CYC: cyclophosphamide; ANF: anifrolumab; ABA: abatacept; Sc: subcutaneous.

*Press release Nov 2016: CHABLIS-SCI has failed to reach the primary outcome

### 1.15.1 Anti-B-cell therapies

Rituximab (RTX) is an anti-CD20 chimeric mouse/human B-cell depleting monoclonal antibody widely used for treatment of B-cell lymphoma, rheumatoid arthritis and granulomatosis with polyangiitis (formerly called Wegener’s disease). CD20-negative plasmacytes and long-lived plasma cells are not affected by RTX treatment, thereby explaining why serum immunoglobulin titres rarely drop and why specific immune protection (e.g. against tetanus toxoid) is maintained. RTX was first tested by several expert groups as rescue therapy for
lupus and LN patients refractory to standard immunosuppression (Looney, 2004; Anolik, 2004; Leandro, 2002; Gunnarsson, 2007; Tokunaga, 2007; Jonsdottir, 2008; Diaz-Lagares, 2012). Two regimens have been used, the so-called lymphoma regimen (375mg/m2 of BSA every week for four consecutive weeks, together with IV CYC) or the rheumatoid arthritis regimen (1 gm, twice, two weeks apart, without IV CYC). These small series suggested that RTX can be very efficacious in refractory lupus, with an effect on serological parameters, clinical outcomes, and renal biopsy. Rituximab has an acceptable safety profile, although a concern has been raised based on two cases of progressive multifocal leukoencephalopathy (Molloy, 2012). However, since that initial report no further cases have been published. B-cell depletion usually occurs within 2 weeks after the first infusion and B-cell repopulation after 3 to 40 months. Flares of disease activity have been reported in about 40% of treated patients, mostly concomitant with B-cell reconstitution. Retreatment with RTX was found to be efficacious and safe (Turner-Stokes, 2011). However, it is not clear whether patients should be pre-emptively re-treated at the time of reconstitution of B-cells. Based on this experience two randomized clinical trials were done: EXPLORER in general lupus (Merrill, 2010a) and LUNAR in LN (Rovin, 2012). Both studies, in which RTX was used as an add-on therapy, failed to show superiority of RTX over standard of care. These negative results, although they may well indicate that RTX is not truly effective in SLE, have been attributed to a number of limitations in study design, such as the selection of inadequate outcome measures and co-medications that may have masked the real benefit of RTX. Two studies are in the pipeline to further define the role of RTX in the treatment of LN. One, entitled RING, is testing the hypothesis that RTX is efficacious in LN patients who failed to achieve a sufficient renal response after at least 6 months of standard immunosuppression. The other, entitled RITUXILUP, is based on the results of an open series of 50 LN patients treated with an oral GC-free regimen, i.e. two pulses of 500 mg IV methylprednisolone and two doses of 1 g RTX, both given two weeks apart, followed by MMF. Renal response rate in these patients, who did not receive oral GCs, was similar to that reported in trials using standard GC therapy (Condon, 2013). The currently recruiting RITUXILUP randomized trial is aimed at testing the non-inferiority of RTX over oral GCs in LN patients treated with two pulses of 500 mg IV methylprednisolone and MMF.

Ocrelizumab (OCR), a humanized anti-CD20 monoclonal antibody, was tested in the BELONG LN trial, as an add-on induction therapy superimposed to GCs and MMF or GCs and Euro-Lupus IV CYC. The trial was terminated early due to a high rate of serious infections in the MMF/OCR group (Mysler, 2013).

Epratuzumab (EPR) is an anti-CD22 monoclonal antibody that acts as a CD22/BCR modulator. More specifically, binding of EPR to CD22 favours the co-localization of CD22 with the BCR, thereby promoting the inhibitory effect of CD22 on BCR signalling (risen threshold). B-cell depletion is much less stringent with EPR compared to RTX. EPR was first tested in ALLEVIATE-1 and ALLEVIATE-2, which were prematurely stopped due to drug supply issues but showed some efficacy (Wallace, 2013). In ENBLEM, a Phase IIb placebo-controlled dose-ranging randomized short-term (12 weeks) trial using a composite endpoint as primary outcome
measure, the BILAG-based Combined Lupus Assessment (BICLA), a beneficial effect was observed in patients given a cumulative dose of 2,400 mg (Wallace, 2014). However, EPR failed in the two pivotal phase III EMBODY studies.

1.15.2 Anti-cytokine therapies

Belimumab (BEL) is a fully humanized monoclonal antibody that binds BlyS (B cell activating factor), a cytokine that stimulates B-cell survival, development and differentiation into plasma cells. Increased levels of BlyS are observed in lupus prone mice as well as in SLE patients. After a promising Phase II dose-ranging trial (Wallace, 2009), two multinational pivotal Phase III trials (BLISS-52 and BLISS-76) demonstrated a statistically significant benefit for the addition of BEL to standard of care in terms of reducing disease activity, flare rates and GC sparing (Navarra 2011; Furie 2011). Both BLISS trials used as primary endpoint a new composite index named the Systemic Lupus Erythematosus Responder Index (SRI) that combines the SELENA-SLEDAI with the British Isles Lupus Assessment Group (BILAG) and the Physician’s Global Assessment. Patients with severe active LN and CNS disease were excluded from both trials. Despite a high response rate induced by standard of care, both trials reached their primary endpoints, as did the BLISS-SC trial in which subcutaneous belimumab was tested (Stohl, 2017). Post-hoc analyses indicated that BEL was more efficacious in patients with higher disease activity, anti-dsDNA positivity, low complement or GC treatment at baseline (van Vollenhoven, 2012). Another post-hoc analysis showed that BEL was most effective in musculoskeletal and mucocutaneous domains (Manzi, 2012). While BEL was EMA-approved in 2011 for the treatment of lupus patients with clinically and serologically active disease and inadequate response to standard therapies, the optimal place of BEL remains to be further tuned (Hahn, 2013). Reassuring long-term safety data are now available (Ginzler, 2014) and a LN trial and a trial in patients of black ethnicity is currently in the pipeline. In serologically active anti-dsDNA positive patients with persistent disease manifestations despite low-dose GCs, HCQ and another immunosuppressant, a course of BEL is warranted with re-evaluation after 6 months. Of note, 1 case of progressive multifocal leukoencephalopathy has been reported in a belimumab-treated patient (Fredericks, 2014).

Other BlyS blocking agents are currently being tested, such as atacicept, a receptor construct that inhibits BlyS and APRIL (Ginzler, 2012) or blisibimod (anti-BlyS peptibody). Development of tabalumab (a monoclonal antibody targeting soluble and membrane-bound BlyS) was halted based on the fact that only one of the two pivotal Phase 3 trials met its primary outcome (Merrill, 2016; Isenberg, 2016).

Type I interferons (IFN) play a pivotal role in the pathogenesis of SLE (Rönnblom, 2006). Several molecules were currently developed to block this pathway (Lauwerys, 2013a). A RCT with the anti-IFN monoclonal rontalizumab failed to demonstrate clinical efficacy (McBride, 2012), but small studies with sifalimumab (anti-IFNα) looked promising (Merrill, 2011; Petri, 2013) and a large phase II trial achieved its primary endpoint.
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(Khamashta, 2016). The IFNα kinoid (a biomolecule designed to induce natural immunity against the cytokine) did not show clinical efficacy in a very small trial (Lauwerys, 2013b). The anti-IFN receptor monoclonal anifrolumab raises many hopes, based on positive Phase II results across several outcome measures. Two dosages (300mg and 1000mg) were tested against placebo in moderate- to severe lupus in addition to standard therapy. The primary endpoint, an SRI response with sustained reduction of steroids <10 mg/day occurred more frequently with both doses and achieved statistically significance with the 300 mg dose, and several secondary outcomes were also met (Furie, 2017). A prespecified secondary analysis in the type 1 interferon “high” population (those with higher IFN-related gene transcripts in peripheral blood leukocytes) showed even stronger results. Herpes zoster and influenza infections were reported more frequently in the anifrolumab groups. A phase III trial is ongoing.

Anti-IL6 sirukumab (Szepietowski, 2013), anti-IL6 receptor tocilizumab (Illei, 2010) and anti-TWEAK BIIB023 were all tested in very small trials but are unlikely to be developed further in SLE. Anti-TNF therapies have never been properly evaluated in SLE, but some experiences with infliximab in a few refractory cases suggested unacceptable safety risks (Aringer, 2009).

1.15.3 Inhibition of co-stimulatory molecules

Activation of (autoimmune) B cells and production of (auto)antibodies depend on optimal co-stimulation through several pairs of transmembrane proteins, such as CD40/CD40L and CD80-86/CD28. Inhibition of these pathways has therefore been tested in SLE.

Two different humanized monoclonal antibodies targeting CD40L have been developed: BG9588 and IDEC 131. A study of the BG9588 monoclonal anti-CD40L antibody in SLE patients with diffuse proliferative glomerulonephritis was terminated early because of thrombotic events, despite an observed reduction of proteinuria, haematuria and anti-dsDNA antibodies (Boumpas, 2003). The anti-CD40L monoclonal IDEC 131 was safe in a Phase I trial (Davis, 2001) but not superior to placebo in a Phase II study (Kalunian, 2002).

Abatacept (ABA) is a CTLA4-Ig fusion protein that binds to CD80/86, thereby preventing its interaction with CD28 on T-cells. The drug is approved for RA. A RCT with abatacept in non-renal SLE failed (Merrill, 2010). ABA was not superior to placebo in LN patients on a background of MMF and GCs for the induction of a complete renal response at 12 months (Furie, 2014). However, using other definitions of renal response, differences in favour of ABA were seen (Wofsy, 2013a), but in a subsequent trial ABA was again not superior to placebo (when given on a Euro-Lupus IV CYC/AZA background) (Wofsy, 2013b).

1.15.4 Other new therapies

Laquinimod (LAQ) is an antigen-presenting cell modulator that skews T cells towards an anti-inflammatory phenotype characterized by increased production of IL-10 and down-regulation of proinflammatory cytokines.
In a small randomized controlled trial, LAQ was found to induce more renal remission compared to placebo, but the difference was not statistically significant (Jayne, 2013).

Lupuzor (LUP) is a peptide (also known as P140) originating from the small nuclear ribonucleoprotein U1-70K. It was shown to display tolerogenic and immunomodulatory effects in preclinical lupus models, i.e. inhibition of T-cell reactivity against self-peptides. It was recently tested in SLE patients and found to induce significantly more SRI responses compared to placebo (Zimmer, 2013).

1.16 Hormonal contraception and hormonal replacement therapy

The use of oestrogens in SLE patients raises safety concerns due to the theoretical risks of disease flares and thromboembolic complications. Two randomized controlled trials, performed in patients with inactive or stable disease without a history of thrombosis, suggest that the use of combined oral contraceptives, containing 30-35 mcg of ethynyl oestradiol, does not increase the incidence of flares, nor the rate of thrombotic events (Petri, 2005; Sanchez-Guerrero, 2005). In patients with the antiphospholipid syndrome (excluded in the study by Petri et al., but not in the trial performed by Sanchez-Guerrero et al.) and/or a history of thrombosis, preference must however be given to other forms of contraception (Culwell, 2009). For patients with SLE in need of chronic anticoagulation a progestin-releasing intrauterine device is likely the ideal contraceptive method.

Prior to the unexpected early termination of the Women’s Health Initiative (WHI) trial of continuous conjugated equine oestrogens (CEE) and medroxyprogesterone acetate (MPA), the prevailing view was that hormone replacement therapy (HRT) was a low-risk intervention. Studies in SLE patients, questioning the safety of hormone replacement therapy (HRT) mainly stem from that era. Nowadays, risks (including breast cancer) and potential benefits of HRT need to be carefully weighed on the basis of individual patient characteristics. In SLE, in the HRT-SELENA trial, 0.625 mg of conjugated oestrogen daily plus 5 mg of medroxyprogesterone for 12 days per month was compared to placebo. Severe flares were not more frequent in the treated group but there were significantly more mild and moderate flares (relative risk: 1.34). Moreover, as in the general population, thromboembolic events were more common, although the difference was not statistically significant (Buyon, 2005). Of note, the trial excluded patients with high-titre anticardiolipin antibodies, lupus anticoagulant, or a previous history of thrombosis, who should not be given HRT. This said, HRT studies in SLE have been performed with oral oestrogens, and it is not known what the effect is of currently available regimens.
2. THERAPEUTIC PROTOCOLS FOR SPECIFIC ORGAN INVOLVEMENT

The therapy of SLE must be chosen based on the complexity of the disease and individual patient characteristics. International organizations such as the European League Against Rheumatism EULAR and the American College of Rheumatology ACR have issued treatment recommendations which may be helpful to the clinician and ensure uniform standards of care (Bertsias, 2008; Bertsias, 2012; Hahn, 2012). Treatment of SLE is guided by the type and the severity of each disease manifestation. Unless biomarkers become available that will allow us to predict to which drug a given SLE patient will respond, we mostly use a “trial and error” approach, of course with full knowledge of available data. Thus, systemic treatment of mild SLE, such as mild mucocutaneous or musculoskeletal involvement, is based on the administration of a short-course of low-dose GCs (0.1-0.2 mg/kg/day) and longer-term antimalarial drugs (mainly HCQ 200-400 mg/day). As already discussed, withdrawal of GCs is a priority and antimalarials are therefore often prescribed long-term irrespective of disease severity. Moderately severe SLE (e.g. more severe mucocutaneous and musculoskeletal disease or serositis) is generally treated with a short-course of medium dose GCs (0.2-0.5 mg/kg/day), promptly tapered to lower dose. In patients who are GC-dependent (i.e. whose disease tends to relapse as soon as the dose of GCs is decreased), it is advised to start a steroid-sparing immunosuppressant, the choice of which depends on the type of organ involvement. In case of arthritis, MTX (or LEF) may be preferred; in case of haematological disease or serositis, AZA might be a good candidate, as well as BEL in selected cases. Severe lupus (e.g. proliferative lupus nephritis, CNS involvement or severe thrombocytopenia) is best treated by a combination of pulse IV methylprednisolone followed by oral GCs (0.5 mg/kg/d) and MMF or IV CYC to induce a prompt response. When this goal is achieved, maintenance therapy with the less toxic immunosuppressant (AZA, MMF) is mandatory, given the high relapse rate. Refractory lupus needs special attention and is likely best managed in expert centres. For such patients, RTX and other biologic therapies are additional options. The following paragraphs specifically deal with certain organ involvements and summarize our best knowledge. They should not be applied “à la lettre” but should serve as a guide for optimal care. Of note, treatment of the antiphospholipid syndrome associated with SLE is discussed in another chapter.

2.1 Renal involvement

When untreated, LN may lead to renal failure with a major impact on survival and quality of life. Renal damage is a predictor of mortality in SLE and recurrent flares are associated with worse long-term outcomes (Bruce, 2015). In most cases a renal biopsy is pivotal to guide therapy. Glomerular lesions are graded according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification criteria (Table II) (Weening, 2004). Importantly, not all LN patients need to be treated aggressively, and renal pathology may avoid both under- and overtreatment. Thus, patients with Class I or II LN should be treated by optimal renal protection (ACEI/ARB) and HCQ and do not need immunosuppression, in contrast to patients...
with proliferative disease (Class III and IV). Pure membranous LN (Class V) raises some specific treatment issues.

**Table II: Implication of histology grading for the therapy of LN**

<table>
<thead>
<tr>
<th>ISN/RPS</th>
<th>Pathology</th>
<th>Signs</th>
<th>Risk for ESRD</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No hypercellularity</td>
<td>Low proteinuria</td>
<td>Very low</td>
<td>ACEI/ARB, HCQ</td>
</tr>
<tr>
<td></td>
<td>Mesangial ID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Mesangial hypercellularity</td>
<td>Low proteinuria</td>
<td>Very low</td>
<td>ACEI/ARB, HCQ</td>
</tr>
<tr>
<td></td>
<td>Mesangial ID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>Endo/extra capillary hypercellularity</td>
<td>Proteinuria, Renal impairment</td>
<td>10-20% with treatment; high risk without treatment</td>
<td>ACEI/ARB, HCQ, GC and other IS</td>
</tr>
<tr>
<td></td>
<td>Subendothelial ID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Widening of BM spikes</td>
<td>Proteinuria, Renal impairment</td>
<td>&lt;10%</td>
<td>ACEI/ARB, HCQ, GC and other IS (selected cases)</td>
</tr>
<tr>
<td></td>
<td>Sub-epithelial ID</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


The main treatment goal in LN is to achieve a prompt response because absence of an early response (6 months) is a poor long-term prognostic factor (Houssiau, 2004; Tamirou, 2016). It was recently demonstrated in two studies that achievement of proteinuria < 0.7-0.8 g/day at 12 months was the best predictor of long-term renal outcome (Dall’Era, 2015; Tamirou, 2015). The current paradigm is to induce a response with an intensive approach using potentially toxic drugs for a short period of time and to maintain the response with a less aggressive immnosuppressant for the long-term. This said, complete renal response rates after 6 months of induction therapy remain low with current therapies (in most studies below 30%), which means that there is room for improvement. Similarly, relapses occur in more than 20-40% of patients (according to length of follow-up) despite maintenance therapy, indicating that further research is needed. Prognostic factors include non-white race, poor socioeconomic status, uncontrolled hypertension, high activity and chronicity on biopsy, renal impairment at baseline and poor initial response to therapy (Austin, 1995). Existing guidelines for the treatment of lupus nephritis include the ACR and EULAR/ERA-EDTA recommendations (Bertsias 2013, Hahn 2012). A comprehensive overview of LN treatment was recently published (Zampeli, 2017).

### 2.1.1 Induction treatment

Three different immunosuppressive regimens can be proposed for patients with Class III/IV LN, namely
i) NIH IV CYC (0.75-1g/m² monthly x 6) combined with IV methylprednisolone and oral GCs (Austin, 1986; Boumpas, 1992; Gourley, 1996; Illei, 2001);

ii) Euro-Lupus IV CYC (500 mg every two weeks x 6) combined with pulse IV methylprednisolone (3 daily pulses of 750 mg) and oral GCs (prednisolone 0.5 mg/kg/d) (Houssiau, 2002) or

iii) MMF (2-3 g/day) (Chan, 2000; Ginzler, 2005; Ong, 2005; Appel, 2009).

The Euro-Lupus Trial showed similar efficacy between option i and ii, although the patients were mostly of Caucasian descent and with moderate nephritis (Houssiau, 2002). Another aspect in the original trial was the start of maintenance therapy with AZA, which started after 3 months in the low dose CYC group and after 12 months in the high dose CYC group where 2 extra quarterly pulses of CYC were given. Results after 10 years’ follow-up have been published and are comparable (Houssiau, 2010). Finally, it should be stressed that the Euro-Lupus regime is also efficacious in LN patients presenting with more severe disease at baseline and in a more racially diverse LN population, as recently demonstrated in the US-based ACCESS trial (Wofsy, 2013).

All RCTs comparing NIH IV CYC to MMF concluded that the two regimens are equally toxic and efficacious, at least in the short and medium term, even for severe LN patients (Tang, 2008; Rovin, 2013; Appel 2009; Ginzler 2005). This was also the conclusion of a Cochrane systematic review (Henderson, 2012) comparing MMF to CYC as induction (and also MMF vs AZA as maintenance). A recent Bayesian network analysis even showed higher remission rates and more favourable safety profile with MMF (Lee, 2015). That said, MMF is more patient-friendly, does not interfere with fertility and can be readily monitored by measurements of mycophenolic acid serum titers. Lower response rates to IV CYC (compared to MMF) have been reported in Hispanics and Blacks (Isenberg, 2010). This does not mean that IV CYC should be withdrawn from the armamentarium of LN. Very long-term data (at least 10 years) are only available so far for LN patients treated with IV CYC. Importantly, IV CYC treatment ensures optimal adherence, especially the Euro-Lupus IV CYC regime because patients are seen every fortnight in the clinic. The Euro-Lupus regime was also tested against MMF in an Asian LN population and no differences could be observed (Rathi, 2016).

AZA induction therapy has been compared to NIH IV CYC. While no more cases of ESRD were observed in the AZA group, there were more renal relapses and more chronic changes on repeat renal biopsies in the AZA group (Grootscholten, 2006; Grootscholten, 2007; Arends, 2012). Except in selected cases (e. g. for toxicity concerns regarding IV CYC and MMF or because of onset of LN during pregnancy), AZA is not recommended as induction therapy (Bertsias, 2012).

Tacrolimus has been studied against MMF in Chinese patients with AZA maintenance and appeared non-inferior, although a trend towards more renal flares and renal function decline with tacrolimus was observed during the follow-up 5 years (Mok, 2016). The combination of MMF and TAC was superior tot IV CYC for achieving a complete renal remission in another Asian study (Liu, 2015).
2.1.2 Maintenance treatment

Two drugs are mainly used for maintenance therapy in LN: AZA (ideally 2-2.5 mg/kg/day) and MMF (usually 2 g/day). The long-term quarterly high-dose IV CYC NIH maintenance regime cannot be recommended anymore, given an unacceptable rate of premature gonadal failure (Boumpas, 1993). AZA and MMF have a very reasonable toxicity profile for long-term use and have been compared in two RCTs: MAINTAIN (Houssiau, 2010b; Tamirou 2016) and ALMS (Dooley, 2011). While in the latter, a multi-ethnic study, MMF was shown superior to AZA to prevent renal relapses, this was not the case in the former, an European-based trial with mainly Caucasian patients. The design of these two trials are different and their results should therefore not be compared head-to-head. Rather, we would suggest, as recommended by the EULAR (Bertsias, 2012) and the ACR (Hahn, 2012), that the two drugs can be used as maintenance therapy of LN, an opportunity since not all patients will respond to the same drug. Patients planning pregnancy should not use MMF which is absolutely contraindicated, at least during the first 3 months. Calcineurin inhibitors are an alternative to AZA or MMF in selected cases. Their stringent antiproteinuric effect, through their effect on podocytes is of interest, as well as the possibility to use them during pregnancy. Nevertheless, their toxicity profile (hypertension, renal impairment, effects on lipid profile, tremor, hirsutism, gum hyperplasia, etc.) and the rebound of proteinuria after their withdrawal explain why we do not propose them as first line maintenance drugs in LN.

An understudied topic is when to stop immunosuppression, as very few studies have addressed this pivotal question (Moroni, 2006). In the absence of data it seems prudent to maintain AZA or MMF for at least several years after remission, or at least very good disease control, is achieved. Of course, each patient’s individual situation must be considered. Most experts feel that GCs can be discontinued relatively soon after a full response has been achieved, but this will also depend on the presence of extra-renal manifestations.

2.1.3 Membranous LN

Membranous lupus glomerulonephritis (ISN/RPS Class V LN) is characterized by sub epithelial immune deposits. It can exist in isolation or be associated with proliferative Class III/IV disease. In the latter cases, most physicians consider that the presence of proliferative lesions guides therapy. Moreover, patients treated for proliferative disease sometimes switch to membranous LN, discovered on repeat kidney biopsy performed because of persisting proteinuria.

Treatment of pure membranous LN does probably not differ from that of idiopathic membranous nephropathy. Based on the nephrology experience, for patients with mild proteinuria a “watchful waiting” approach with optimal blockade of the angiotensin renin aldosterone system is usually appropriate. In patients with severe proteinuria, immunosuppressants are usually added, combining GCs with either MMF, AZA or CNI. In a controlled trial performed at the NIH, patients with pure membranous LN received (A) CSA...
2.1.4 Biologics in LN

As already alluded to, none of the biological therapies tested so far has demonstrated effectiveness in LN as add-on therapy, superimposed to standard of care. The future of targeted therapy in LN may therefore well be elsewhere, e. g. as a GC-sparing agent or for the treatment of refractory cases not responding to at least 6 months of standard immunosuppression, as currently tested in the RING study.

2.1.5 Optimal care for LN patients

The principles of optimal care for LN are summarized in Table III

Table III: Optimal care for LN patients

| Early detection and complete baseline evaluation, including renal biopsy |
| Education on the long-term risks and the treatment goals |
| Follow-up in specialized Lupus Clinics |
| Identification of non-adherence to therapy |
| Minimize glucocorticoids |
| Early treatment switch in case of insufficient response after 6 months |
| Optimal renal protection (BP: ≤120/80 mm Hg; antiproteinuric therapy) |
| Prevention of cardiovascular disease (smoking cessation, weight control, BP control, lipids) |
| Prevention of GC-induced bone loss |
| Immunization (HPV, influenza, Streptococcus pneumoniae) |

2.1.6 Renal replacement therapy

Between 10 and 20% of LN patients will require renal replacement therapy (RRT), the lower figures being observed in RCTs and the higher in the real world. It is of critical importance to look for these data in the very long-term, since LN usually starts in young patients. In some very refractory cases, it may be wiser to step down immunosuppression, when the battle is lost anyway, in order to avoid further toxicity. Haemodialysis is preferred by certain expert nephrologists based on a higher rate of infectious events in LN patients treated by peritoneal dialysis, but this view is not unanimously shared (Rietveld, 2008). Most LN patients with ESRD are suitable candidates for renal transplantation (RT) (Nossent, 1991). Some recommend waiting to transplant to
allow for quiescence of the SLE-related immune activity. Other data suggest that longer waiting times to transplant may be associated with equivalent or worse, not better, graft outcomes among LN-ESRD patients (Plantinga, 2015). More studies are needed to clarify the potential confounding effect of lupus disease activity on the observed associations. When feasible, the ideal setting is pre-emptive grafting (before ESRD is reached) with a living donor (Lochhead, 1996; Ward, 2000). Recurrence of LN in the graft is possible but rare (1-4%) (Moroni, 2005; Stone, 1997). On the whole, graft survival has been reported to be similar compared to other ESRD groups and lower than in other glomerular diseases. The factors associated with a poor outcome of RT are listed in Table IV.

### Table IV: Poor prognostic factors in renal transplantation for SLE

<table>
<thead>
<tr>
<th><strong>Cadaveric transplantation</strong></th>
<th>Living donor RT is associated with better graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity</strong></td>
<td>Black patients have a poorer graft survival</td>
</tr>
<tr>
<td><strong>Anti-phospholipid positivity</strong></td>
<td>Thrombotic events are much more frequent in RT recipients with APL antibodies</td>
</tr>
<tr>
<td><strong>Disease activity after RT</strong></td>
<td>Persistent lupus disease activity requires further immunosuppression but is associated with more infectious events</td>
</tr>
<tr>
<td><strong>Clinical status at the time of RT</strong></td>
<td>Poor general medical condition deleteriously impacts graft and patient survival after RT</td>
</tr>
<tr>
<td><strong>Dialysis duration</strong></td>
<td>Long-term dialysis risk factor for graft failure? (unclear)</td>
</tr>
</tbody>
</table>

#### 2.2 Central nervous system involvement

Neuropsychiatric involvement in SLE (NPSLE) is characterized by a variety of clinical manifestations and its pathogenesis and assessment are complex and debated. As a consequence, designing controlled trials is extremely difficult and treatment of NPSLE strongly relies on the treating physician’s clinical experience (Hanly, 2005). Treatment of NPSLE can be symptomatic, based on experience with, for example, anticonvulsants, antipsychotic or antidepressant drugs and/or aimed at controlling pathogenetic mechanisms, such as inflammation and thrombosis. EULAR recommendations have been published to guide in this process (Bertsias, 2010).

Faced with a patient with possible NPSLE, two issues are critical. First, is it really related to lupus? Many clinical manifestations are vague and can be best explained by alternative hypotheses, such as infection (viral, opportunistic, bacterial, TB), drug toxicity and even fatigue or depression. CNS imaging, cerebrospinal fluid examination and cognitive tests are not always helpful, thereby making the picture even more complicated. Other demyelinating diseases, such as multiple sclerosis, need to be ruled out (Magro Checa, 2013). The second dilemma deals with the mechanism involved: is it inflammation or thrombosis mediated by anti-phospholipid antibodies? Or do both play a role? While this question might look trivial in theory, the answer is always difficult at the bedside. Yet, treatment is very different!
The data currently available, albeit scarce, support the use of IV methylprednisolone and IV CYC pulse therapy as first choice treatment in severe NPSLE, after exclusion of manifestations which could be attributed to the presence of anti-phospholipid antibodies (Trevisani, 2006, Cochrane review). In a retrospective analysis, CYC was found efficacious in treating patients with organic brain disease (55% of the patients in that study), stroke (35%), neuropathies (10%), persistent headache (10%), seizures (9%), psychiatric manifestations (26%), transverse myelitis (16%) and cranial neuropathies (13%). Improvement was observed in 61% of the patients, stabilisation in 29% and deterioration in 10% (Neuwelt, 1995). Only 1 non-blinded randomized controlled trial compared the efficacy of pulse IV methylprednisolone versus IV CYC in treating NPSLE. CYC was administered as monthly pulses (0.75 g/m²) for 6 months and then every 3 months for one year. CYC was significantly more effective in the treatment of NPSLE than pulse IV MP, particularly in treating patients with seizures, optic neuritis, peripheral neuropathy, and brainstem disease (Barile-Fabris, 2005). In acute severe NPSLE, such as transverse myelitis, prompt installation of combined therapy with pulse IV methylprednisolone and IV CYC should be considered strongly.

In refractory NPSLE cases, other treatments can be tried, without strong evidence base. Case reports suggest that PE (Neuwelt, 2003; Bartolucci, 2007), IVIG (Sanna, 2008), RTX (Narvaez, 2011) and even intrathecal dexamethasone and MTX (Zhou, 2008) can be useful.

In patients with SLE and the anti-phospholipid syndrome, the approach should clearly be different, with oral anticoagulation strongly advised to maintain an INR value around 2.5-3 (Ruiz-Irastorza, 2005). The possible role of anti-platelet agents in these patients is under discussion, as is the intensity of anticoagulation (INR) and the duration of therapy. Given the effects of antimalarials on platelet aggregation, HCQ should be considered as well. In Table V, a tentative treatment scheme for NPSLE is proposed.

### Table V: Management of NPSLE

<table>
<thead>
<tr>
<th>Inflammatory mechanisms *</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulse IV MP and IV CYC</td>
<td>GC tapering</td>
</tr>
<tr>
<td></td>
<td>Symptomatic therapy</td>
<td>Steroid-sparing immunosuppressant: AZA, MMF(?)</td>
</tr>
<tr>
<td></td>
<td>Plasma exchange in refractory cases</td>
<td>Symptomatic therapy</td>
</tr>
<tr>
<td></td>
<td>Rituximab in refractory cases</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombotic mechanisms *</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral anticoagulation (target INR 2.5-3.0)</td>
<td>Oral anticoagulant (target INR 2.5-3.0)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic therapy</td>
<td>Symptomatic therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low-dose aspirin</td>
</tr>
</tbody>
</table>

* beware that both mechanisms can play a role at the same time
2.3 Mucocutaneous involvement

Expertise is needed to make a proper distinction between acute, subacute and chronic cutaneous lupus erythematosus (CLE), not to mention lupus profundus, chilblain lupus and lupus tumidus (Okon, 2013). The differential diagnosis is broad: some more common conditions, such as rosacea, need to be ruled out. In patients with cutaneous involvement, photo protection is very important and strict sunscreen adherence and adequate clothing must be emphasised and/or application of a sun protection factor ≥ 50 spf about 20 minutes before sun exposure (Kuhn, 2011a). Topical GCs, topical tacrolimus and antimalarials are first-line therapies. Topical GCs must be prescribed and preference must be given to the potent fluorinated derivates (instead of hydrocortisone) (Jessop, 2009). They should however be used with “holiday” periods (e.g. two weeks on and one week off) to avoid skin atrophy and telangiectasias. Topical CNI have been introduced more recently with excellent results reported for tacrolimus ointment (Tzung, 2007; Kuhn, 2011b). Antimalarials are the standard systemic therapy of CLE. HCQ is most frequently used, but in more severe cases of chronic CLE, better results have been reported with chloroquine, quinacrine and with combinations of different antimalarials (Meinao, 1996; Toubi, 2000). When antimalarials fail, MTX has been shown effective in a few RCTs and case series, and AZA, THA and dapsone can be efficacious in difficult to treat cases (Kuhn, 2016). Belimumab showed efficacy in a subgroup analysis of the BLISS trials for mucocutaneous parameters (Manzi, 2012). THA deserves special attention given its impressive effects in refractory chronic CLE (Cortez-Hernandes, 2012), with the caveats already mentioned before. There is one case report of the successful use of tocilizumab (anti-IL 6) in a case of refractory SLE with lupus tumidus and urticarial vasculitis (Makol, 2012). The type I IFN system has also become a potential target in cutaneous disease, since skin lesions are characterized by a strong expression of IFN-regulated proinflammatory cytokines. Anifrolumab showed significant improvement of disease activity including skin lesions, suggesting efficacy in cutaneous lupus (Furie, 2015).

2.4 Musculoskeletal involvement

Non-erosive polyarthritis, affecting predominantly finger joints, wrists and knees, occurs in the vast majority of SLE patients (about 90% of cases) and is one of the earliest disease manifestations. Low-dose GCs and antimalarials are the first choice treatment for polyarthritis, together with NSAIDS in the absence of contraindications. In more severe GC-dependent cases, MTX can be prescribed based on several trials and case series (Gansauge, 1997; Carneiro 1999; Islam, 2012; Rahman 1998; Winzer, 2010), as well as LEF (Remer, 2001; Wu, 2013), AZA or belimumab (BLISS trial). Less frequently, SLE patients develop a deforming arthropathy, called Jaccoud’s arthropathy, which mostly appears insidiously and induces much disability in daily life activities. While the classical acute polyarthritis is usually promptly responsive to therapy, few interventions (including rehabilitation procedures) are helpful in Jaccoud’s arthropathy.
Osteoporosis has long been neglected in SLE, based on the wrong assumption that young women were protected against GC-induced bone loss by their female hormones. SLE patients, however, have an increased risk of osteoporotic fractures (1.2-4.7 fold) compared to the general population and the risk is further increased by a longer disease duration, GC use in the previous 6 months, and previous osteoporotic fractures (Bultink, 2014). Another cohort study detected prevalent vertebral fractures in 18-50% of SLE patients and revealed low 25-hydroxyvitamin D serum levels, low body mass index and baseline use of antimalarials as associated with bone loss in SLE (Bultink, 2016). Smoking, renal and ovarian failure, and reduced exercise are traditional risk factors often encountered in SLE patients. These data show that this comorbidity cannot be neglected and risk factors should be actively assessed and if possible treated, for example by vitamin D3 and calcium supplementation, exercise and smoking cessation. The use of anti-osteoporosis medication in premenopausal women has unfortunately remained poorly studied despite the clear need for data in patients with severe SLE starting at younger ages.

Avascular osteonecrosis (AON) is frequent in SLE, mainly in patients treated with high-dose GCs (Houssiau, 1998) and is a major contributor to musculoskeletal damage, as assessed by the SLICC-DI. The best prevention is to avoid high doses of GCs as much as possible.

2.5 Haematological involvement

Mild leukopenia is frequent when SLE is active and does not require treatment per se. Anaemia is also common in SLE and might be unrelated (iron deficiency being common in women of childbearing age) or linked to the disease, either through chronic inflammation (active SLE commonly induces erythroblastopenia), renal impairment, or haemolysis (much rarer). In case of erythroblastopenia, treatment of lupus usually corrects the anaemia. Active haemolysis (low haptoglobin, elevated LDH, high reticulocyte count) usually requires high dose GCs, promptly tapered, together with a GC-sparing agent, such as AZA or MMF. In relapsing or refractory cases, RTX and recently belimumab have been shown useful. Mild thrombocytopenia, as for example often seen in the presence of antiphospholipid antibodies, does not require specific therapy. Severe thrombocytopenia can be life-threatening and requires high dose GC treatment (pulse IV methylprednisolone and oral prednisolone) and/or IVIG. Again, steroid-sparing agents should be prescribed if remission cannot be maintained with low dose GCs. RTX and splenectomy can be considered in refractory/relapsing cases.

When thrombotic thrombocytopenic purpura (or thrombotic thrombocytopenic microangiopathy) occurs in the setting of pre-existing SLE the syndrome is typically associated with the presence of antiphospholipid antibodies. This diagnosis should always be excluded in a lupus patient with pancytopenia, mainly acute thrombocytopenia, haemolysis, an excess of schistocytes on blood smears, renal failure and other micro-thrombotic manifestations (e. g. skin necrotic lesions). This microangiopathy, sometimes present within the
frame of the so-called “catastrophic antiphospholipid syndrome” requires aggressive therapy combining plasma exchanges, anticoagulants and GCs.

The macrophage-activation haemophagocytic syndrome (Rosado, 2013) is a potentially fatal complication of SLE, mainly in children (Parodi, 2009; Benet, 2012), and should always be excluded in critically ill patients with fever, pancytopenia, elevated liver enzymes, coagulopathy (hypofibrinogenaemia), elevated ferritinaemia and high triglyceride levels. Bone marrow aspiration shows the typical picture of macrophages phagocytosing haematopoietic cells. The syndrome is a cytokine storm due to unabated macrophage activation. Prompt intervention is required with IV methylprednisolone and oral GC. In severe cases, IV CYC, CYA and cytostatic drugs such as etoposide may be useful adjunct therapies.

2.6 Serositis

The treatment of SLE-related serositis is mostly based on the usual treatment for active SLE. Medium doses of GCs are usually needed. Other immunosuppressants have been used successfully, such as AZA or MTX. Pleuro-pericardiocentesis may be required in case of large effusions or to rule out other diagnoses in difficult cases.

3. COMORBIDITIES

3.1 Cardiovascular disease

In 1976, Urowitz et al. first described a “bimodal mortality pattern” in SLE, with a first peak due to the disease itself and a second wave related to cardiovascular disease (CVD) (Urowitz, 1976). This pivotal observation was largely confirmed by many expert groups and it is now clearly established that SLE patients are at high risk of CVD (Manzi, 1997; Roman, 2003). While traditional factors (smoking, hypertension, diabetes, hyperlipidaemia, etc.) play an obvious role and must be reviewed (Table VI), they do not fully explain the risk, thereby lending support to the possibility that unabated lupus-induced inflammation per se is a risk factor. In this respect, one should expect that GC use would be associated with improved cardiovascular prognosis but the data prove exactly the contrary: prednisone doses of more than 10 mg/day increase the cardiovascular risk two fold and doses of more than 20 mg/day fivefold (Magder, 2012), probably due to the well-known metabolic effects of GCs. Taken together, disease control is essential but this goal should be achieved with the lowest possible cumulative dose of GCs. Antimalarials contribute to a more favourable lipid (Rahman, 1999) and glucose (Petri, 1994) profile and display some antithrombotic activity (Ruiz-Irastorza, 2006), by reducing the binding of antiphospholipid anti-beta2-glycoprotein I complexes to phospholipid bilayers (Rand, 2008). Finally, primary prevention with aspirin and statins should also be considered. In vitro and in vivo studies suggest that statins have direct anti-inflammatory, antithrombotic and plaque-stabilizing effects via a number of mechanisms, besides their well-known lipid-lowering effect. However, a well-designed randomized controlled trial (the LAPS trial) with atorvastatin failed to demonstrate prevention of progression of coronary artery calcium
content and carotid intima thickness in adult SLE patients (Petri, 2011), and therefore it is at present unclear if the use of statins can be advised in the absence of hypercholesterolemia.

**Table VI: Cardiovascular risk factors and targets in SLE.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Target</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>&lt;120 mmHg syst; &lt;80 mmHg diast</td>
<td>ACEI/ARB as first choice</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt;100 mg/dl or &lt;130 mg/dl</td>
<td>Statins - HCQ</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Fasting blood glucose &lt;7.0 mmol/l</td>
<td>Weight loss – Metformin – HCQ</td>
</tr>
<tr>
<td>Smoking</td>
<td>Stop smoking</td>
<td>Nicotine replacement – Bupropion – Varenicline</td>
</tr>
<tr>
<td>Obesity</td>
<td>Body mass index &lt;25 kg/m²</td>
<td>Diet – Aerobic exercise</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>&lt;85 µg/dl</td>
<td>Folic acid supplements</td>
</tr>
</tbody>
</table>

3.2 Other comorbidities

Relevant comorbidities and the main preventative measures are shown in Table VII.

**Table VII: Comorbidities in SLE.**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>See. Table VI</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Less GCs</td>
</tr>
<tr>
<td></td>
<td>Calcium salts and D3 supplementation</td>
</tr>
<tr>
<td></td>
<td>Bisphosphonates in selected cases</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
</tr>
<tr>
<td></td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Infections</td>
<td>Less GCs</td>
</tr>
<tr>
<td></td>
<td>Anti-influenza immunization (yearly)</td>
</tr>
<tr>
<td></td>
<td>Anti-pneumococcal immunization (q5 years)</td>
</tr>
<tr>
<td></td>
<td>Anti-HPV</td>
</tr>
<tr>
<td>Vitamin D3 deficiency</td>
<td>D3 supplementation (25-OHD3 ≥25 ng/ml)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Exercise</td>
</tr>
<tr>
<td>Malignancy</td>
<td>PAP smears (yearly)</td>
</tr>
<tr>
<td>Secondary fibromyalgia</td>
<td>Exercise</td>
</tr>
<tr>
<td></td>
<td>Pain clinic</td>
</tr>
</tbody>
</table>

Prevention of infections deserves special attention as it is one of the leading causes of death in SLE (Cervera, 2003). Not only opportunistic infections but also common pathogens, such as Streptococcus pneumoniae and Haemophilus influenzae, contribute to mortality. SLE patients must be vaccinated against relevant pathogens (but note that the use of live vaccines may be contraindicated if they take GCs and/or other immunosuppressants). Current data suggest that vaccination of SLE patient is safe and efficacious (Kuruma, 2007; Battafarano, 1998), although serum antibody titers may be lower, but sufficiently protective; older concerns that vaccination could trigger lupus flares have not been born out in carefully designed studies.
4. ADHERENCE TO THERAPY

Not surprisingly, many young lupus patients do not take the many pills we prescribe to treat their L or LN, as recently demonstrated by HCQ blood titers measurements. Some patients take their medications only for a few days before the visit the clinic, a common phenomenon in chronic diseases known as “white coat compliance”. Thus, a hypertensive patient who wants to please his physician will take a few blood pressure-lowering pills for a short period of time preceding the visit and will be declared compliant since his/her blood pressure levels measured the day of the visit will be deemed satisfactory. In contrast, patients taking HCQ once in a while will be unmasked by whole blood HCQ measurements. In a retrospective analysis, more lupus flares were observed in patients who were less compliant (Costedoat-Chalumeau, 2007). Non-adherence can be addressed in clinical practice by repeated explanations given to lupus patients and their relatives on the reasons why each drug is prescribed, and by sketching the global treatment plan as soon as the treatment is started, so that patients understand that many of the drugs will be progressively withdrawn or their dose tapered, even if some will be prescribed for several years. In this respect, the help of a nurse practitioner in our busy lupus clinics can be most valuable.
SUMMARY POINTS

Glucocorticoids are responsible for some of the damage observed in SLE. Their use should be limited to the shortest possible period of time. Intravenous pulse methylprednisolone therapy is useful for acute life-threatening cases and may allow reduction of peak oral GC dose.

Antimalarials should be considered for all SLE patients, even in the absence of overt active clinical manifestations. Their benefits include flare prevention, amelioration of some SLE symptoms, and beneficial effects on lipid and glucose profile. They are also believed to have antithrombotic properties and may reduce cardiovascular risk. Antimalarials are safe in pregnancy and need not be discontinued.

In lupus nephritis, intravenous pulse cyclophosphamide (either the low-dose Euro-Lupus regimen or the higher-dose NIH regime) and mycophenolate mofetil are equivalent induction therapies. Azathioprine and mycophenolate mofetil can both be used for long-term maintenance treatment. Yet, further improvement is eagerly awaited since complete renal remission rate is only 30% after induction therapy and since up to 40% of patients suffer from renal relapse.

Belimumab is the first biologic approved for the treatment of lupus. It was shown superior to standard of care in two pivotal trials. Yet, its precise place in daily practice needs to be further defined. Other biologic therapies are currently being tested, with promising results for the type-1 interferon inhibitor anifrolumab.

Despite two negative randomized trials, rituximab deserves further investigation, based on many reports suggesting efficacy in severe refractory cases of lupus nephritis and of some other lupus manifestations. Several trials are currently ongoing under the umbrella of the Lupus Nephritis Trials Network (www.lupusnephritis.org).

Kidney transplantation is an important option for patients with end-stage renal disease. Recurrence of lupus nephritis after renal transplantation is rare and graft survival is by and large comparable to a control population.

Patients with SLE are at increased cardiovascular risk. Traditional risk factors should therefore be monitored and controlled by lifestyle modification (e.g., diet, weight control, smoking avoidance) and by specific treatments (e.g., statins, antihypertensive).

Patients with SLE, especially those treated with GC and other immunosuppressants, are at high risk of infections. Immunization against influenza and Streptococcus pneumoniae is strongly recommended. Osteoporosis is another major comorbidity to evaluate and manage if necessary.

Lack of adherence to therapy may contribute to treatment failure.
References


