RHEUMATOLOGY

Rheumatology 2010;49:2243–2254
doi:10.1093/rheumatology/keq269
Advance Access publication 7 September 2010

Review

The management of peripheral blood cytopenias in systemic lupus erythematosus

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Abstract

Haematological complications are frequently seen in SLE. Anaemia, leucopenias and thrombocytopenia may result from bone marrow failure or excessive peripheral cell destruction, both of which may be immune mediated. Drugs and infection are other common causes. In this review, we will focus on the diagnosis and management of immune-mediated leucopenias and thrombocytopenia in SLE. The roles of bone marrow examination and the measurement of antibodies against leucocytes and platelets are discussed. Although many patients do not require specific treatment for cytopenias in SLE, CSs remain the mainstay of treatment. Other conventional therapies include AZA, CYC and human normal immunoglobulin. More recently, MMF has found a role as a CS and CYC-sparing agent. We also review B-cell depletion in the management of thrombocytopenia associated with SLE and other novel therapies including thrombopoeitin receptor agonists.

Key words: Lupus, Leucopenia, Lymphopenia, Neutropenia, Thrombocytopenia, Bone marrow, Mycophenolate, Cyclophosphamide, Rituximab, Romiplostim.

REVIEW

Introduction

Haematological involvement is common in SLE. Haematological disorder is included in the ACR Classification criteria for SLE. This includes haemolytic anaemia with a reticulocytosis, leucopenia ($<4.0 \times 10^9$/l) or lymphopenia ($<1.5 \times 10^9$/l) on two or more occasions, or thrombocytopenia ($<100 \times 10^9$/l) in the absence of offending drugs [1].

In this review, we will focus on the diagnosis and management of immune-mediated leucopenias and thrombocytopenia in SLE. The pathophysiology and management of anaemia in SLE has been reviewed recently [2]. The association between aPLs and SLE will not be covered, but the interested reader is directed to two recent reviews on the management of the APS [3, 4]. The causes of cytopenia in SLE are listed in Table 1.

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Submitted 12 March 2010; revised version accepted 14 July 2010.

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Leucopenia

Leucopenia is a typical feature of SLE, and may occur as a result of lymphopenia, neutropenia or a combination of the two. Leucocytosis *per se* is uncommon, and more often than not relates to the presence of infection or CS therapy. The prevalence of lymphopenia in SLE ranges from 20 to 81% and its degree may correlate with disease activity [5, 6]. Both T and B lymphocytes are reduced, while in contrast NK cells are typically increased [7, 8]. Although there are numerous reports of lymphotoxic antibodies in SLE (frequency 36–90%) [9–11], their pathogenic significance remains unclear, as does the importance of their measurement in clinical practice. Reduced surface expression of complement regulatory proteins CD55 and CD59 has also been implicated in the pathogenesis of lymphopenia in SLE [12, 13]. Deficiency of these glycophospatidyl inositol-anchored proteins may make these and other cells susceptible to complement-mediated lysis. In contrast, we have previously observed increased expression of CD55, but not CD59, on peripheral blood leucocytes in SLE [14]. This may serve as a protective mechanism against complement-mediated attack in active disease. There is also increasing evidence for a role of endogenous production of type 1 IFNs in the pathogenesis of neutropenia and lymphopenia in SLE [15]. Elevated serum levels of IFN-α are observed in SLE, this correlating inversely with leucocyte numbers [16].

Table 1 Causes of cytopenia in SLE

Thrombocytopenia
Immune mediated
Acute, severe
Chronic, mild
APS
Infection
Drug induced
Common: AZA, CYC, MTX
Rare: HCQ, MMF, CSA, NSAIDs, statins, ACE inhibitors
TTP
Disseminated intravascular coagulation
Amegakaryocytic thrombocytopenia
Myelodysplasia
Uraemia
Lymphopenia
Immune mediated
Infection, particularly viral
Drug induced
Neutropenia
Immune mediated
Infection
Drug induced
Common: AZA, CYC, MTX
Rare: MMF, CSA, HCQ
Myelodysplasia
Myelofibrosis

Neutropenia is also a common feature of SLE, with a prevalence in the order of 47%, and this may be mediated by anti-neutrophil antibodies [6]. Impaired function of the mononuclear phagocytic system, allowing sensitized cells to remain in the circulation, may in part compensate for this [17]. G-CSF levels are characteristically increased in SLE patients with neutropenia [18]. This may reflect reduced sensitivity of myeloid cells to G-CSF or the presence of immunoglobulin G (IgG) and immunoglobulin M (IgM) anti-G-CSF antibodies [19]. The increase in serum TNF-related apoptosis-inducing ligand in SLE may also contribute to neutropenia through excessive neutrophil apoptosis [20]. Although autoimmunity is the most likely explanation for neutropenia in SLE, other pathologies, such as myelofibrosis, may also on occasion have a role [21]. As with lymphopenia, when mild, neutropenia often has no clinical consequences, but on occasion may be associated with life-threatening sepsis [22]. Neutropenia in SLE also is frequently drug related, and unlike thrombocytopenia, is not associated with increased mortality [23].

Thrombocytopenia

Thrombocytopenia has a reported prevalence ranging from 7 to 30% in large series of patients with SLE [24–27]. Increased peripheral destruction of platelets, associated with the presence of anti-platelet antibodies, is the most likely pathogenic mechanism [28–30]. aPLs may also be implicated, along with antibodies against thrombopoietin (TPO) [30, 31], the TPO receptor c-Mpl [32, 33] and CD40L [34]. Increased TPO levels have also been reported. Thrombocytopenia in SLE may be acute in onset and extremely severe. This presentation is usually related to active disease in other organ systems and tends to be CS responsive. A more chronic form, less related to disease activity, is also common, and typically less responsive to CS therapy. ITP may predate SLE in up to 16% of patients [35, 36], appearing up to 10 years before SLE becomes clinically apparent [36].

Thrombocytopenia in SLE is often associated with haemolytic anaemia, the presence of other cytopenias and with aPLs [37]. Although an association may be seen between anti-dsDNA antibodies and haemolytic anaemia [25], this association is not apparent in cases of thrombocytopenia [37]. In addition to high-dose CS therapy, thrombocytopenia is an independent risk factor for increased mortality in SLE [26]. In a retrospective study of 126 patients with SLE, late-onset thrombocytopenia was associated with an increased mortality [6]. No association was found with aPLs and the increase in mortality was not attributable to thromboembolic events. A more recent retrospective study of 632 patients found a particularly high prevalence of thrombocytopenia, which was present in 58% at the time of diagnosis [38]. An association with disease activity, increased mortality and hypocomplementaemia was apparent.

Thrombocytopenia may also occur in other contexts in SLE, for example, as a complication of drug therapy with, for example, immunosuppressants such as AZA and rarely HCQ. Thrombotic thrombocytopenic purpura (TTP) is also well recognized, but is fortunately rare [39, 40]. TTP complicating SLE can be difficult to diagnose because of overlapping features between the two disorders. Thrombotic micro-angiopathic haemolytic anaemia is also reported in association with SLE [41], characterized by thrombocytopenia, micro-angiopathic haemolytic anaemia, fever, neurological symptoms and kidney involvement.

An approach to the investigation of cytopenias in SLE

A detailed drug history is essential. This should take into account both drugs prescribed directly for the condition and those for its complications, such as statins, antibiotics and ACE inhibitors. Leucopenia and thrombocytopenia may complicate the treatment of SLE with AZA, MTX and, rarely, CSA, MMF or HCQ. Neutropenia may follow pulsed CYC, with a nadir usually occurring on Day 10 post-infusion, this being partly dose dependent. Macrophage activation syndrome should be considered if cytopenia develops rapidly, especially in juvenile SLE. The patient should be examined carefully for signs of infection, thrombocytopenia and lymphoproliferative disease. If neutropenia is present and the patient is pyrexial at $>38.0^{\circ}$C, blood cultures and samples from other sites should be sent for microbiological examination. In cases of pancytopenia or suspected pure red cell aplasia, parvovirus B19 serology should also be performed [42].

The specific investigation of a cytopenia in SLE should begin by examination of the peripheral blood film, which is often overlooked. This may merely confirm thrombocytopenia, but may reveal an alternative explanation such as platelet clumping, causing an artefactual reduction in platelet count. An increase in the proportion of large platelets may be seen in patients with thrombocytopenia [43]. Identification of the morphology of lymphocytes may be diagnostic of specific lymphoproliferative disorders. Co-existent anaemia requires analysis of haematinics, a reticulocyte count and direct Coomb's test. Other appropriate investigations include a serum lactate dehydrogenase (LDH), liver function tests, immunoglobulins and serum protein electrophoresis. Peripheral blood gene rearrangement studies (immunoglobulin heavy chain gene or T-cell receptor gene rearrangement) should be considered if there is a high index of suspicion of a lymphoproliferative disorder.

The measurement of anti-platelet and other antibodies in routine clinical practice is more controversial. A number of assays are available for the measurement of anti-platelet antibodies, mainly directed against glycoproteins IIb/IIIa and Ib/IX [29]. Due to their cost, limited availability and the time taken to obtain a result, the measurement of anti-platelet antibodies using such techniques is probably not necessary. However, their use should be considered in cases of severe thrombocytopenia, particularly if refractory to treatment. There is some evidence that their level may correlate with disease activity. When platelet levels normalize in treated patients, anti-platelet antibodies may decrease significantly or become undetectable [28, 44]. The absence of anti-platelet antibodies does not, however, exclude an autoimmune aetiology for the thrombocytopenia in an individual patient with SLE.

IgG and IgM anti-neutrophil and anti-lymphocyte antibodies may also be measured by IIF using flow cytometry. This will determine the cellular specificity and immunoglobulin class of the antibody. The specificity of anti-lymphocyte antibodies may further be investigated by an ELISA for HLA Class I antibodies. The neutrophil chemiluminescence test is also used by some laboratories [17]. This measures the response of human monocytes to antibody-opsonized neutrophils from the patient, a positive result supporting the presence of neutrophil-reactive antibodies. The limitations of the assays used to measure anti-neutrophil antibodies in patients with neutropenia have been reviewed recently [45]. aPLs may also be associated with thrombocytopenia and haemolytic anaemia and are measured routinely in most laboratories. Other antibodies of possible pathogenic relevance in lupus-associated cytopenia, such as those against G-CSF [19] and the TPO receptor [32] are not routinely measured.

Bone marrow (BM) aspiration and trephine should be considered in all cases of severe or persistent leucopenia or thrombocytopenia in a patient with SLE. Likewise, BM examination is essential in cases of pancytopenia, particularly if the patient is receiving myelotoxic therapy such as AZA, MMF or CYC. Specific features may be present in the marrow to suggest drug-induced myelotoxicity. AZA, for example, may cause aplastic anaemia, erythroid hypoplasia and megaloblastic changes. BM examination may also reveal haematological malignancy and haemophagocytosis. BM culture is indicated in fever of unknown origin in immunosuppressed patients with SLE. Common abnormalities in the BM in patients with SLE include increased haemopoietic precursors suggestive of peripheral destruction or alternatively SLE-induced hypocellularity, an increase in reticulin and a plasmacytosis [46, 47]. BM necrosis with stromal alterations is also frequent. In patients with thrombocytopenia, a number of megakaryocyte abnormalities may be seen. These cells may be clustered, hypolobulated and pyknotic, and may have a denuded cytoplasm. We have observed an increase in the frequency of apoptotic bodies in the BM of SLE patients [48]. This supports the hypotheses that the marrow may be a target organ in the disease and that normal clearance mechanisms are defective and/or overwhelmed in SLE [49].

Treatment of cytopenias in SLE

Leucopenias and thrombocytopenia are often mild in SLE and require no specific drug therapy. Corticosteroids remain the treatment of choice in the initial management of more severe cases and have been used in this context for >30 years [50]. With thrombocytopenia, treatment should be considered if bleeding or severe bruising are present, or with platelet counts $<50 \times 10^9$/l. There are no randomized controlled trials of the use of corticosteroids in the treatment of peripheral blood cytopenias in SLE. In cases of severe thrombocytopenia ($<20 \times 10^9$/l), prednisolone tapering from 1 mg/kg/day should be commenced. Pulsed methylprednisolone may also be used, although there is probably no advantage in its use over high-dose oral CSs, whereas the risk of serious adverse effects such as avascular necrosis is increased [51, 52]. Of note, the presence of antibodies against the TPO receptor may be associated with a poorer response to CSs [33].

AZA is traditionally introduced as a steroid-sparing agent in the treatment of thrombocytopenia in SLE [53, 54]. However, there are no randomized controlled trials of its use in this context. CSA is an alternative immunosuppressive drug in the treatment of lupus-associated cytopenias [55]. In an open-label trial in 16 patients with SLE, platelet and leucocyte levels returned to normal in those patients with thrombocytopenia or leucopenia treated with CSA 3–5 mg/kg/day for an average treatment period of 30 months [56]. However, we would not advocate the use of these doses because of the risk of nephrotoxicity and prefer doses up to 2.5 mg/kg/day, with close monitoring of renal function and blood pressure. Further, others have recommended the use of even lower doses [57]. Its success as a steroid-sparing agent in lupus-associated thrombocytopenia, with minimal side effects, has been reported recently [58]. Despite this, the association of hypertensive and renal complications with ciclosporin suggest that it

should be used cautiously and patients carefully monitored. Treatment with combination of prednisolone and HCQ may be an adequate alternative for controlling thrombocytopenia in many patients [59].

If treatment of thrombocytopenia with prednisolone or steroid-sparing agents is unsuccessful, splenectomy should be considered. The response to splenectomy for lupus-associated thrombocytopenia is generally favourable [60–63]. Only one study has suggested a poor outcome [64]. Given the important role for the spleen in the clearance of immune complexes, a risk of a flare in disease activity has been suggested following splenectomy in SLE [35], but this is not generally born out in practice. The importance of appropriate prophylactic measures against infection following splenectomy in SLE cannot be overemphasized [65]. This includes the use of the pneumococcal, haemophilus influenza type B, meningitis C and influenza vaccines and prophylactic antibiotics such as penicillin V, particularly in patients with additional chronic hypocomplementaemia. Pneumococcal vaccination may need to be repeated after 5 years, particularly if antibody levels have declined.

IVIG

IVIG can be very effective in some patients with lupus-associated thrombocytopenia. Its use in this context and for other manifestations of SLE has recently been reviewed [66]. IVIG is well established as a treatment option in ITP, and a long-lasting response in lupus-associated thrombocytopenia has been reported [67]. Thrombocytopenia and certain other manifestations of SLE, such as neuropsychiatric disease, appear to respond particularly well to IVIG [68]. Its mechanism of action in SLE is likely to be multimodal. These include down-regulation of autoantibody production, neutralization of pathogenic autoantibodies by anti-idiotypic antibodies, inhibition of complement-mediated damage, modulation of cytokine production, induction of apoptosis in lymphocytes and monocytes, and modulation of both B- and T-lymphocyte function [69]. Further, in ITP, IVIG may both block activatory and up-regulate inhibitory Fcγ receptors [70]. Danazol is another option for the specific treatment of thrombocytopenia in SLE [71–73]. This is generally safe and well tolerated, and like IVIG may be used in pregnancy in this context [74]. The therapeutic dose of IVIG in severe thrombocytopenia complicating SLE is 2 g/kg, usually given in five consecutive daily doses of 400 mg/kg. Maintenance of remission using repeated doses of IVIG in severe thrombocytopenia complicating SLE has also been reported [75].

Refractory cytopenias

The treatment of severe cytopenias and aplastic anaemia in SLE may necessitate treatment with more potent cytotoxics including CYC. CYC therapy (prescribed as 0.75–1.0 g/m^2 body surface area or 10–15 mg/kg), given intravenously every month for at least 4 months appears useful in the treatment of severe lupus-associated thrombocytopenia refractory to standard therapies [76]. Lower doses given more frequently, for example every 2 weeks, are being used increasingly in some institutions, in order to improve tolerability without loss of efficacy. Balancing the risks and benefits of such therapy can be difficult, particularly in the presence of severe neutropenia. However, successful use of high-dose i.v. CYC in the treatment of aplastic anaemia complicating SLE has been reported [77, 78]. BM analysis before therapy is particularly helpful in this setting, with increased erythrocyte or leucocyte precursors in the marrow suggesting a response to therapy being more likely. Furthermore, concurrent use of recombinant human G-CSF (rhG-CSF) and antibiotics reduced the risk of this form of approach [48].

CYC may also form a part of therapy in the management of TTP complicating SLE [39, 79]. TTP may also respond to plasmapharesis in this context [40, 80]. Plasmapheresis has also been used to treat refractory autoimmune thrombocytopenia, pure red cell aplasia, haemophagocytic syndrome and thrombotic microangiopathic haemolytic anaemia complicating SLE [41, 81–83], and has been reported to reverse pancytopenia in five patients with SLE [84–87]. Although anti-thymocyte globulin and anti-lymphocyte globulin are used in the treatment of idiopathic aplastic anaemia, their use in SLE is limited to one case report [88].

Supportive therapy

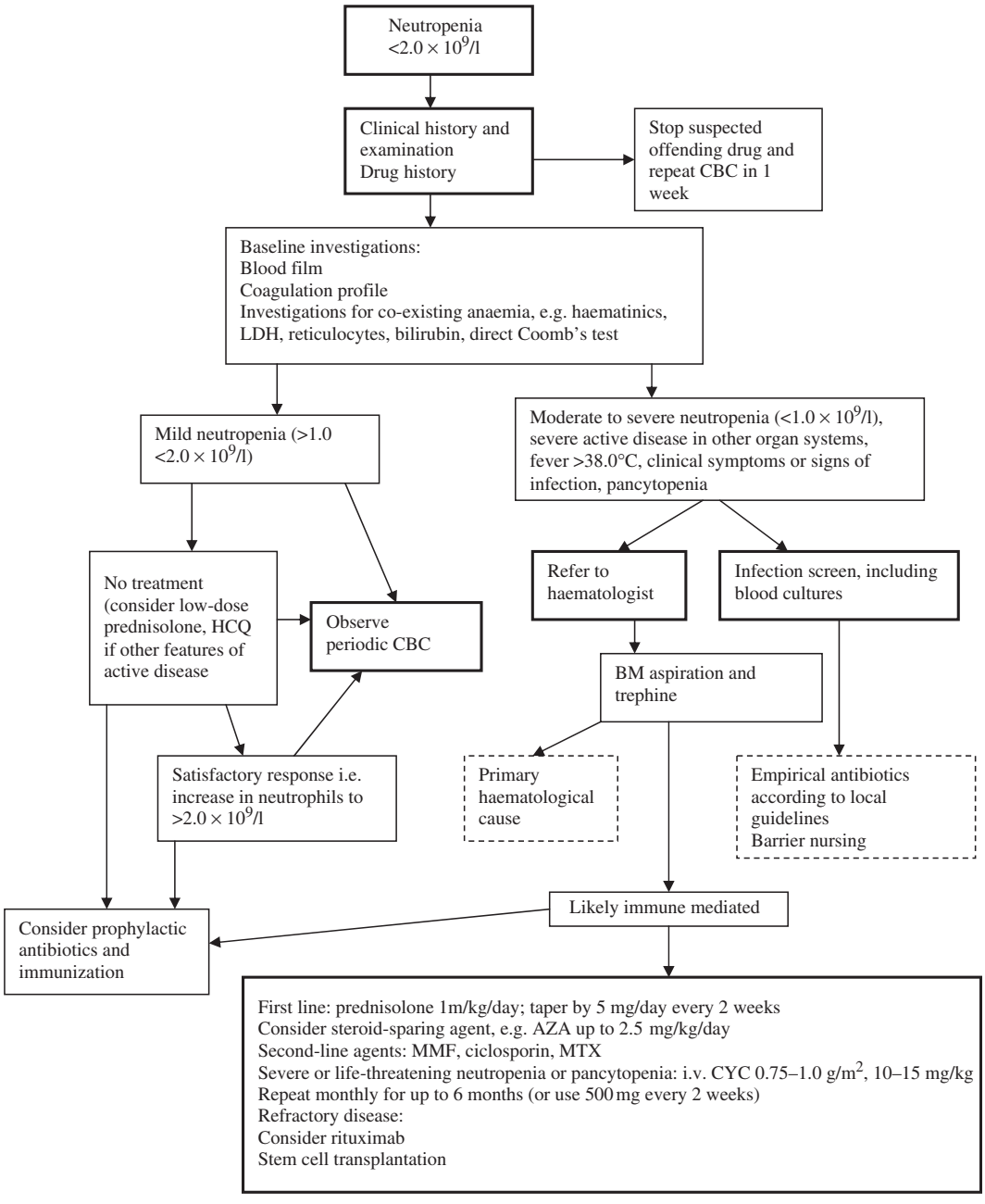
In cases of severe cytopenias complicating SLE, supportive measures may also be required. Platelet transfusions are generally best avoided in immune-mediated thrombocytopenia, but may be required immediately before invasive procedures and surgery with platelet counts $<10 \times 10^9$/l. In febrile neutropenic patients ($\leqslant 1.0 \times 10^9$/l and fever $\geqslant 38.0^\circ$C), reverse barrier nursing and broad spectrum antibiotics should be used. With respect to the choice of antibiotics in the context, local guidelines for patients with neutropenia receiving chemotherapy should be followed. Intravenous tazosin and gentamicin are generally the first-line drugs of choice. If neutropenia is severe (for example, $<0.1 \times 10^9$/l), treatment with rhG-CSF should be contemplated [45]. There is, however, only limited literature addressing the use of rhG-CSF in lupus-associated neutropenia. In one study, rhG-CSF was administered subcutaneously to nine patients with SLE and neutropenia with refractory infections [22]. A rapid increase in neutrophil count was observed, but disease flared in three of nine patients. Others have also observed lupus flares with the use of rhG-CSF [89]. Further, the effect on neutrophil counts may only be temporary, and may be a rationale for concurrent immunosuppression [48]. The management of neutropenia and thrombocytopenia complicating SLE is summarized in Figs 1 and 2.

Newer therapies for cytopenias complicating SLE

MMF

MMF, an immunosuppressive drug widely used in solid organ transplantation, is increasingly used in SLE and

FIG. 1 Flow chart for the management of neutropenia in SLE. CBC: complete blood count.

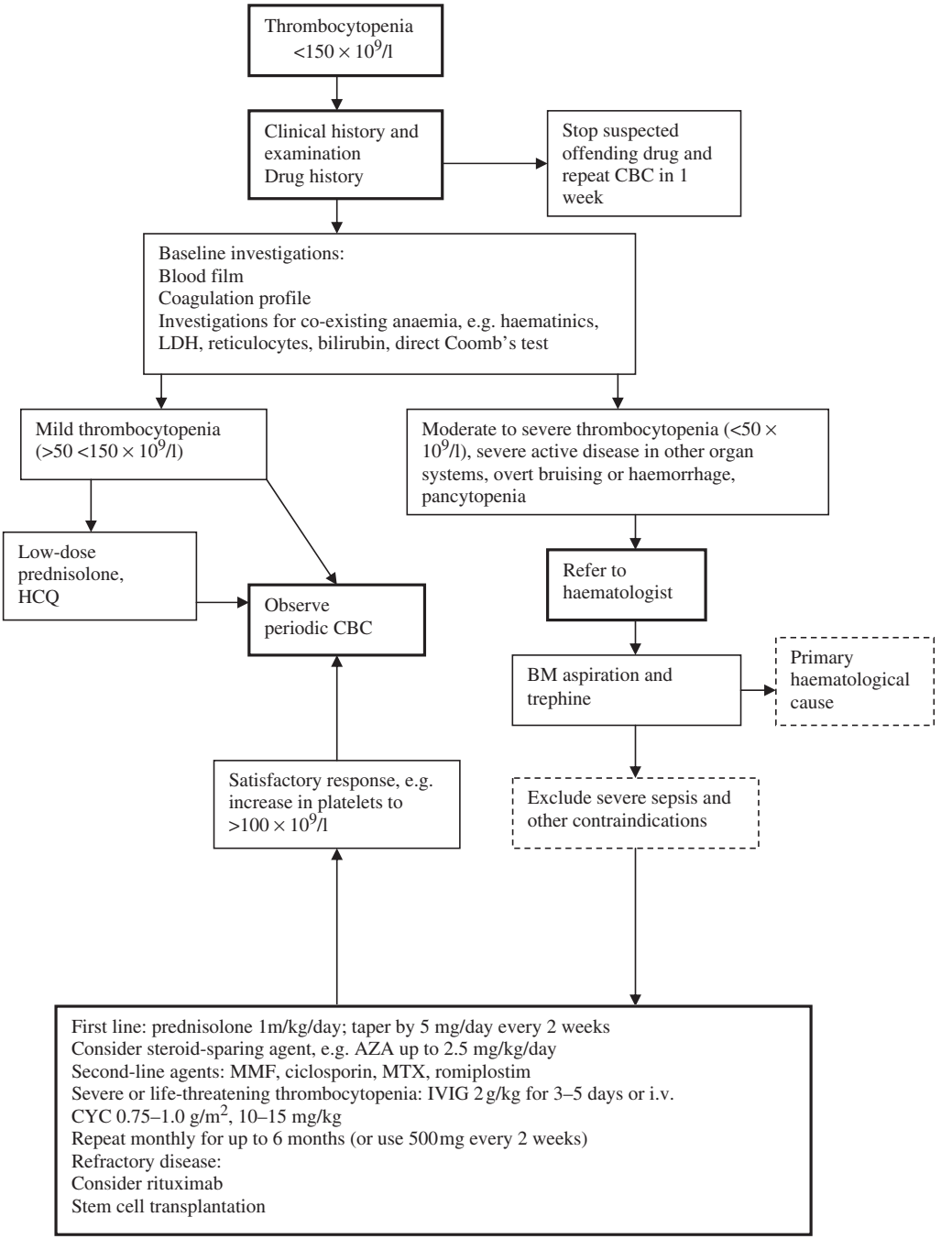


other autoimmune diseases. MMF is a pro-drug of mycophenolic acid, an inhibitor of inosine-5′-monophosphate dehydrogenase, and has several immunosuppressant actions, which have been reviewed recently [90]. MMF is rapidly becoming an alternative therapy for the induction and maintenance of lupus nephritis, with less toxicity than i.v. CYC [91, 92]. There are also reports of its use in the management of refractory haemolytic anaemia and thrombocytopenia complicating SLE [93–96]. Further, MMF has also been used in conjunction with CSA in the treatment of pure red cell aplasia complicating SLE [97]. Its use in SLE beyond glomerulonephritis is likely to increase, and it remains a promising therapy for the management of its haematological manifestations.

Immunoablative dose CYC and stem cell transplantation

The treatment of severe and particularly refractory autoimmune diseases has been improved somewhat by the introduction of intense immunoablative immunosuppression using three different approaches. These are allogeneic haematopoietic stem cell transplantation (HSCT),

Fig. 2 Flow chart for the management of thrombocytopenia in SLE.



autologous HSCT (using either marrow or peripheral blood) and high-dose immunoablative immunosuppression without stem cell support. Trials in SLE, including patients with severe haematological manifestations, and in other autoimmune disorders suggest that high-dose immunosuppressive therapy with or without autologous haematopoietic stem cell support can induce remission of previous refractory disease [98–100]. In autologous HSCT, stem cells are mobilized with high-dose CYC and G-CSF. The graft is enriched with CD34-positive selection and re-infused after conditioning with CYC, methylprednisolone and anti-thymocyte globulin. However, a concern with this approach is that autoreactive effector cells infused with the allograft may re-establish autoimmunity [101].

Thus, an alternative approach is the use of high-dose CYC without stem cell transplantation. This has been used successfully in aplastic anaemia and other autoimmune

disorders including SLE [102–104]. Although prescribed primarily for patients with SLE and severe renal or CNS disease, a response to this regimen has been reported in SLE complicated by pancytopenia [104]. Haematological recovery after high-dose CYC without stem cell transplantation is usually rapid and the regimen is well tolerated. It may be an option in severe, refractory haematological lupus as an alternative to monthly i.v. CYC at standard doses.

Anti-B-cell therapies

The central role for B cells in the pathogenesis of SLE provides the rationale for the use of the anti-CD20 monoclonal antibody rituximab in its treatment. CD20 is expressed during the intermediate stages of B-cell development but is lost during the terminal stages, being absent on plasma cells. Rituximab is a chimaeric monoclonal antibody against human CD20, and rapidly depletes peripheral blood CD20-positive B cells via complement-mediated and antibody-dependent cellular cytotoxicity [105]. Although initially used in the treatment of relapsed low-grade B-cell follicular non-Hodgkin's lymphoma, rituximab was subsequently used successfully in the treatment of chronic ITP [106].

In patients with SLE, rituximab has been shown to deplete autoreactive B-cell populations and reduce autoantibody production by plasma cells [107]. Its clinical efficacy has been examined in patients with SLE who were poorly responsive to conventional therapies, but without major organ involvement [108]. When given using a dose escalation protocol of between a single dose of 100 mg/m^2 and four weekly doses of 375 mg/m^2, rituximab led to depletion of B cells that correlated with a reduction in disease manifestations. However, significant alterations were not seen in anti-dsDNA antibody levels. In an open-label study in six patients, all of whom had varying degrees of haematological involvement, rituximab was administered in conjunction with i.v. CYC and high-dose oral CSs [109]. A reduction in DASs was seen, with improvement in haematological parameters, anaemia in particular. A subsequent study of 17 patients with SLE and renal, CNS and haematological involvement demonstrated effective B-cell depletion in 11/17 patients, and a reduction in DASs [110]. Early studies of rituximab in SLE also included patients with severe thrombocytopenia. A particularly favourable response was observed in one patient, with stable platelet numbers over 100×10^9/l for >6 months and disappearance of anti-DNA antibodies [111]. Later reports have confirmed the efficacy of rituximab in SLE-associated thrombocytopenia, including TTP and the rare amegakaryocytic thrombocytopenia [112–116]. Rituximab has also been used successfully in the treatment of autoimmune haemolytic anaemia complicating SLE [116]. We and others have also reviewed the use of this drug in ITP, TTP and haemolytic anaemia [117, 118]. Overall, current data suggest that rituximab is a promising option for the treatment of severe haematological manifestations in SLE, and controlled trials are now indicated.

An alternative approach involves the autoreactive B-cell survival factor B-lymphocyte stimulator (BLyS). BLys, a TNF-related cytokine, can be targeted in a number of ways, such as through decoy receptors and with anti-BLyS monoclonal antibodies. LymphoStat-B (belimumab) is a fully human monoclonal antibody that binds to BLyS with high affinity and neutralizes human BLyS bioactivity *in vitro* and *in vivo* [119]. LymphoStat-B has been tested in a Phase I trial that included 70 SLE patients, and was found to be safe, with no clinically significant differences from placebo in adverse events. It also significantly reduced levels of circulating B cells and anti-dsDNA antibodies. A Phase II trial that includes 449 patients has also recently been reported [120]. There was a longer time to disease flare in patients receiving belimumab compared with placebo and a reduction in anti-dsDNA titres was observed. In a subgroup analysis, patients with serologically active disease responded significantly better to belimumab therapy. Although its effect on cytopenias in SLE is not yet known, it may represent an additional therapeutic approach for their management. Abetimus (LJP 394), which induces tolerance in B cells against anti-dsDNA antibodies, has so far only been investigated for the prevention of renal flares in lupus [121].

Other novel approaches

Eltrombopag is a thrombopoeitin receptor agonist in late-stage development for the treatment of thrombocytopenia. Phase II trials have recently been published examining its role in ITP [122] and in thrombocytopenia associated with hepatitis C infection [123]. In the ITP trial, eltrombopag was administered orally at a dose of 30, 50 or 75 mg daily in 118 patients with platelet counts $<30 \times 10^9$/l for 6 weeks. The primary endpoint was a platelet count $>50 \times 10^9$/l at Day 43. This was achieved in 28, 70 and 81% in the three eltrombopag dosage groups, respectively, compared with 11% in the placebo group [122]. The median platelet counts at Day 43 were 26×10^9/l, 126×10^9/l, 183×10^9/l and 16×10^9/l, respectively. In the two higher dosage groups, bleeding episodes were also reduced. Adverse event rates and severity were similar in all four groups. However, the durability of the response remains unclear, and over the 6-week post-treatment follow-up period platelet counts in the eltrombopag groups gradually return to baseline. Notwithstanding, the drug holds promise for SLE-associated thrombocytopenia and no known interactions occur between eltrobompag and the immunosuppressive agents used in SLE.

Romiplostim (AMG 531) is another TPO receptor agonist that is now licensed for the treatment of chronic refractory immune thrombocytopenia. It consists of an IgG_1 Fc component linked to a peptide domain with four binding sites for Mpl, the TPO receptor. Unlike first-generation recombinant megakaryocyte growth and development factor, romiplostin has no sequence homology with TPO, hence there is less risk of developing antibodies against endogenous TPO. It has high affinity for the TPO receptor and increases megakaryocyte differentiation. It is

administered as weekly subcutaneous injections and the response is dose dependent, peaking at Days 12–15 [124]. In two Phase III placebo-controlled randomized trials, romiplostim was administered weekly in 63 splenectomized and 62 non-splenectomized ITP patients with mean baseline platelet counts of 16×10^9/l for 24 weeks. Sustained platelet response was observed in 16 (38%) of the 42 splenectomized patients receiving romiplostim and none in the placebo arm. Similarly, durable platelet responses were seen in 25 (56%) of the 41 non-splenectomized patients receiving romiplostim compared with only 1 of the 21 patients receiving placebo. Adverse events were reportedly mild but increased BM reticulin that reversed on stopping the treatment was reported in one non-responding patient [125]. Long-term safety has been addressed in an ongoing open-labelled single-arm study. A total of 142 patients with ITP received romiplostim for up to 156 weeks (mean 69 weeks). Eighty-seven per cent of patients responded (platelet count $>50 \times 10^9$/l). Treatment-related adverse events were observed in 9%. BM reticulin was increased in eight patients and thrombotic events in seven (5%) patients. Of the two patients who had regular follow-up, BM biopsies after stopping romiplostim partial resolution of reticulin was seen in one [126].

IL-11 is a thrombopoietic growth factor that induces proliferation of megakaryocyte progenitors and megakaryocyte maturation [127]. There is one report of the use of recombinant human IL-11 in the treatment of severe thrombocytopenia complicating SLE [128]. Anti-CD40 L monoclonal therapies have not yet been shown to be particularly efficacious in SLE and there is concern over an apparent increase in thromboembolic events in treated patients [129]. A role for anti-CD40 L and other therapies targeting co-stimulatory molecules such as CTLA4-Ig in haematological SLE is unclear at present, but further trials are likely to be performed. The use of immune complexes (i.v. anti-D) as an alternative to IVIG in the treatment of autoimmune thrombocytopenia is another potential approach [70, 130]. Intravenous anti-D could also be considered instead of IVIG to treat thrombocytopenia in patients who have not had splenectomy [131].

Conclusion

Peripheral blood cytopenias are common in SLE and their management can be challenging. In many individual cases, they are mild and do not require specific therapy. However, cytopenia may be a marker for active disease in other organ systems and, when severe, may be associated with increased mortality. Although treatment with CSs is often sufficient to control clinically significant leucopenia and thrombocytopenia in SLE, more potent immunosuppression with AZA or CYC may be required. A number of novel therapeutic approaches to the management of cytopenias, including thrombopoeitin receptor agonists and anti-B-cell therapies, in particular, are showing great promise.

Rheumatology key messages

- Autoimmune cytopenias are common in SLE.
- When specific treatment is required, CSs will often suffice.
- Novel therapeutic options include B-cell depletion, MMF and TPO receptor agonists.

Acknowledgements

Disclosure statement: The authors have declared no conflicts of interest.

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