bjh review

State of the art – how I manage immune thrombocytopenia

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Summary

The management of patients with immune thrombocytopenia (ITP) is rapidly evolving. Over the last 15 years, a number of novel treatments have improved practice, with many steroid-sparing agents and a reduction in the progression to splenectomy. Although this has improved clinical care, many therapeutic challenges remain. There is no diagnostic test, no biomarkers to direct treatment and few comparative studies to help management decisions. Development of up to date guidelines is difficult with little high-grade evidence. First line treatment continues to be steroids and intravenous immunoglobulins (IVIG) although both are often poorly tolerated and not curative. Common second line treatments include rituximab, immunosuppressive agents, such as azathioprine and mycophenolate mofetil, and the thrombopoietin receptor agonists romiplostim and eltrombopag. There are no comparative studies to decide between these agents and treatment is generally individualized, depending on comorbidity. Use of splenectomy has declined and is generally reserved for patients with chronic disease, although the exact position of splenectomy is subject to debate. Further understanding of the cause of disease in individual patients may help guide treatment. Randomized controlled studies of common treatments and novel treatments for refractory patients are urgently needed.

Keywords: ITP, romiplostim, eltrombopag, rituximab, MMF.

Introduction

The management of immune thrombocytopenia (ITP) has significantly changed over the last 50 years with a better understanding of the disease and introduction of many steroid-sparing agents. Publication of the 'terms and definitions of ITP' paper in 2009 was an important step in improving management (Rodeghiero *et al*, 2009). It has helped to define ITP and to classify patients into subgroups according to progression of disease (Rodeghiero *et al*, 2009). These definitions have been useful to help design and interpret novel trials. Recognition that the platelet count is less important than overall bleeding symptoms has also improved management by reducing the numbers of patients receiving unnecessary treatment. Finally, the development of steroid- and splenectomy-sparing agents, including intravenous (IV) immunoglobulin and IV Anti-D, rituximab, and the thrombopoietin receptor agonists (TPO-RAs), romiplostim and eltrombopag, have all reduced morbidity. The increase in novel treatments is particularly important, as the morbidity and mortality has historically related as much from infection as from bleeding (Cohen *et al*, 2000; Portielje *et al*, 2001).

However, with an increase in novel treatments there are also more management dilemmas. ITP is a heterogeneous disease and progression of disease and responses to treatment are not possible to predict. The most prominent issues are: how can we identify which patients need treatment, given that most remain asymptomatic despite thrombocytopenia; and, if treatment is needed, which treatment options should be used? Table I outlines some of the questions remaining in ITP. Two current guidelines/consensus documents list a number of treatment options, but with little evidence for individual treatment pathways (Provan *et al*, 2010; Neunert *et al*, 2011).

The heterogeneity of disease and the different responses to treatment may represent different underlying causes of thrombocytopenia in ITP. Initially, ITP was thought to be an antibody-mediated disease (Harrington *et al* 1951) and in many patients, this may be predominant, with premature destruction of antibody-coated platelets. However, a variety of T cell abnormalities have also been described in patients with ITP, including skewing of T helper cells to an autoimmune phenotype (Semple & Freedman, 1991; Ogawara *et al*, 2003; Culic *et al*, 2013; Talaat *et al*, 2014), poor activity of regulatory T cells (Liu *et al*, 2007; Sakakura *et al*, 2007; Stasi *et al*, 2008; Yu *et al*, 2008; Bao *et al*, 2010), or regulatory B cells (Li *et al*, 2012) and also direct killing of platelets by cytotoxic T cells (Olsson *et al*, 2003; Zhang *et al*, 2006). Both antibodies and T cells may also attack megakaryocytes, resulting in reduced platelet production (Kuwana *et al*, 1998; Li *et al*, 2007; Gernsheimer, 2009). It is not clear how these T- and B-cell findings are related or whether antibody or T cell-mediated disease is more prominent in individual patients (Fig 1). Establishing biomarkers to identify these features could help to direct treatment (Barsam *et al*, 2011).

This review will outline some of the management dilemmas in ITP and outline the pathway we currently use in clinical practice.

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Table I. Questions remaining in the management of ITP

Questions in ITP	Studies required
1. Does the patient have ITP?	Better diagnostics: basic science studies of the pathology of ITP
2. Is there a platelet count at which patients should be treated?	Assessment of risk of bleeding and HRQoL and comparison to bleeding tests such as TEG and platelet reticulocytes
3. What first line therapies are likely to induce the greatest remission rate?	RCTs of steroids (different types and doses) *versus* IVIG *versus* nothing, RCTs of TPO-RAs as upfront treatment
4. Which second line treatments give the best long term remission	RCTs of rituximab, MMF and TPO-RAs
5. What is the role of splenectomy in ITP?	Long-term outcome studies assessing both prediction of success and long term toxicity in comparison to medical treatment.
6. What are the long-term risks of immunosuppression or TPO-RAs?	Registry data comparing assessing long term outcome

HRQoL, Health-related quality of life; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; RCT, randomized controlled trials; TEG, thromboelastogram; TPO-RAs, thrombopoietin receptor agonists.

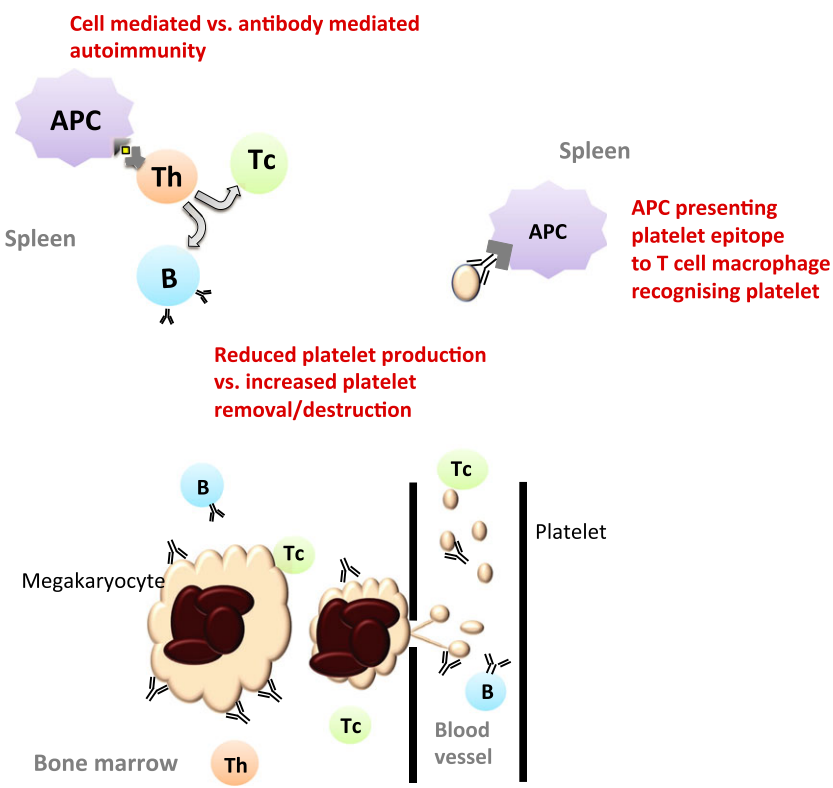

Fig 1. Pathology of immune thrombocytopenia. Immune thrombocytopenia (ITP) is a heterogeneous disease and the primary cause of loss of tolerance is not known. Increasing evidence suggests that the main controller of disease is the T helper cell (Th), with coordination of autoantibody producing B cells and cytotoxic T cells (Tc). These autoantibodies and cytotoxic T cells can cause platelet destruction in the blood and spleen, and/or inhibition of platelet production in the bone marrow. APC, antigen presenting cell.

Management

Diagnosis

Despite identification of a serum-derived thrombocytopenic factor in the 1950s (Harrington *et al*, 1951) and decades of work describing the function of anti-platelet antibodies (APAs), reliable clinical identification of the APA has remained elusive. This may relate to ineffective testing methods or because there are other causes of thrombocytopenia in individual patients (Cines & Millan, 2007). ITP therefore remains a diagnosis of exclusion. Table II outlines the recommended investigations from the consensus document (Provan *et al*, 2010) and the American Society of Hematology (ASH) guidelines (Neunert *et al*, 2011). Measuring helicobacter pylori antigen by stool test is contentious. There is little evidence for causality in the UK population (Stasi *et al*, 2009). However, this has not been fully evaluated and the treatment is short term and without adverse effects. I therefore include it in our diagnostic tests. Measurement of immunoglobulin levels and lymphocyte subsets are important to identify patients with immunodeficiency, particularly before using immunosuppressive agents, including rituximab. It is also important to check the direct antiglobulin test

Table II. Investigations in suspected immune thrombocytopenia

Investigations in patients with thrombocytopenia
Full blood count, reticulocytes, platelet volume and blood film
Renal, liver and bone profile
Immunoglobulins
Lymphocyte subsets
Dilute Russell venom viper test
Anti cardiolipin antibody
ANA ± ds DNA and ENA
Thyroid function tests
Hepatitis B
Hepatitis C
Human immunodeficiency virus
Helicobacter pylori antigen test
Ultrasound scan abdomen (liver disease, splenomegaly)
Investigations which may be helpful in patients with persistent or chronic disease, atypical disease or refractory disease
Bone marrow examination
Antiplatelet antibodies
Cytomegalovirus PCR (blood and urine)
Epstein-Barr virus PCR
Genetic screen for causes of thrombocytopenia
Thrombopoietin levels

ANA, anti-nuclear antibodies; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen; PCR, polymerase chain reaction.

(DAT), hepatitis B antibody status and immunoglobulin levels before giving intravenous immunoglobulin (IVIG) therapy as IVIG can lead to subsequent false positive results.

In patients with refractory disease, especially children, investigations for other viral causes of disease, such as the presence of Epstein–Barr virus (EBV) or cytomegalovirus (CMV) by polymerase chain reaction (PCR) in urine, blood and bone marrow (depending on the relevant virus) can be helpful (DiMaggio *et al*, 2009).

Some investigations have a less clear role in the diagnosis of ITP. For example:

1. Is a bone marrow examination necessary in ITP?. Bone marrow examination is not recommended in patients with typical ITP, particularly in patients who respond well to treatment, by either the most recent ASH guidelines (Neunert *et al*, 2011) or the consensus document (Provan *et al*, 2010). However, this is an important test, especially in patients with refractory disease. The test should include evaluation of cellularity, megakaryocyte abnormalities, B and T cell clonality, and karyotype to look for other causes of thrombocytopenia. This may be particularly relevant at both younger and older ages. I recommend bone marrow examination in: patients over 65 years of age; patients with atypical features, abnormalities on blood film or any other full blood count (FBC) abnormalities; presence of lymphadenopathy/splenomegaly; patients who do not respond appropriately to IVIG and steroids. I also recommend bone marrow examination before using TPO-RAs and in most patients with persistent ITP.

The last two indications are not routine practice. My opinion is that a bone marrow in persistent disease is useful, partly to ensure diagnosis (given the lack of diagnostic test) but also because many of these patients will have ITP for the rest of their lives and some develop new bone marrow disorders later in life (four of our patients have developed myelodysplastic syndrome, myelofibrosis and osteosclerosis 10–20 years after a diagnosis of ITP). Comparison to a bone marrow done early on in diagnosis is very helpful. Although longitudinal studies have not shown bone marrow changes 2–3 years after TPO-RAs, there is still limited follow up on these patients.

2. Does the measurement of anti-platelet antibodies (APA) have a role in the management of ITP?. Measurement of APAs is not recommended in either consensus document of ASH guidelines. However, although APAs are not sensitive for ITP (up to 40% of patients have no detectable antibodies), glycoprotein-specific assays are highly specific for ITP (Warner *et al*, 1999; McMinn *et al*, 2003) and in patients with refractory disease, a strongly positive test helps to reassure that the disease is antibody mediated. Furthermore, the type of APA may predict the responses to steroids or IVIG (Zeng *et al*, 2012; Li *et al*, 2015) and may predict chronic disease and bleeding (Grimaldi *et al*, 2014). Development of better assays and correlation with response to treatment is necessary.

3. What is the value of thrombopoietin testing?. Patients with ITP have normal or only slightly higher than normal thrombopoietin levels. In contrast, patients with other causes of thrombocytopenia, in particular aplastic anaemia, have very raised levels of thrombopoietin (Aledort *et al*, 2004; Makar *et al*, 2013; Kuter *et al*, 2014). Although not routinely available, this may become an important tool in the diagnosis of ITP, although it is not recommended in the current ASH guidelines (Neunert *et al*, 2011).

4. Can genomics help with diagnosis?. Whole exome and genome sequencing has established a number of genetic causes for thrombocytopenia (Macaulay *et al*, 2005; Lentaigne *et al*, 2016). In patients with refractory ITP or with atypical features, alternative causes of thrombocytopenia should be considered; sequencing of relevant pathological genes known to cause thrombocytopenia may be an important approach to clarifying these cases.

Finally, other aspects of the platelet count can be helpful. The percentage immature platelet fraction is usually higher in patients with ITP (Barsam *et al*, 2011), and the mean platelet volume is lower in ITP when compared to the hereditary thrombocytopenias (Makar *et al*, 2013). Neither tests are in routine clinical use, or recommended by the guidelines. Mean platelet volume is especially useful to identify hereditary causes of thrombocytopenia (small platelets in X-Linked thrombocytopenia and large platelets in MYH9 disorders).

If patients fail to respond to appropriate treatment, reassessment of the diagnosis is important.

Decision to treat

Only a proportion of patients with ITP develop severe bleeding. In patients who do not have overt bleeding, but have persistently low platelet counts, the risk of future bleeding is not clear. The risk of intracranial haemorrhage (ICH) increases with age. However, the toxicities of treatment also increase with age (Michel *et al*, 2011). The platelet count gives some indication of bleeding risk, however not all patients bleed at low platelet counts (Arnold, 2012). Bleeding tests, such as thromboelastometry, may have a role in predicting bleeding but are not routinely used (Greene *et al*, 2014; Frelinger *et al*, 2015).

As a general guide, adults who have persistent platelet counts above 30×10^9/l are not at risk of serious bleeding and, unless there is another reason for them to require a higher platelet count, patients can be managed with observation alone. We usually recommend treatment in adults who have platelet counts persistently less than 10×10^9/l. The decision to treat adults with platelet counts between 10×10^9/l and 30×10^9/l depends on other factors: age, activity, psychological impact of low platelets, fatigue, bleeding and bruising symptoms, other comorbidity, anaemia suggestive of significant bleeding and whether a tolerable treatment can be found (Table III outlines treatment triggers).

Co-morbidity also influences treatment decisions, for example, the presence of cardiac stents or cardiac valves, requirement for anti-platelet agents or anticoagulation. General recommendations are to keep the platelet count above 50×10^9/l if anticoagulation or anti-platelet agents are needed. However, this is not always possible, and patients can have myocardial infarcts at platelet counts less than 30×10^9/l. Consideration of the risks of bleeding compared to the risk of thrombosis must be made on an individual basis. Specific platelet counts may be less useful than bleeding symptoms.

Table III. Treatment triggers

Treatment triggers
Blood blisters in mouth
Organ bleeding (Intracranial haemorrhage, gastrointestinal)
Haematuria
Anaemia and microcytosis caused by bleeding
Menorrhagia
Impact on life
Loss of work or school activities
Potential treatment triggers
Persistent severe thrombocytopenia
Significant bruises and petechial
Depression
Fatigue
Anxiety
Risk activity (skiing)
Stage of life related to considered risk
Co morbidity
Inability to review case regularly or to access emergency treatment (off shore working)

How to treat

The "terms and definitions document" categorises ITP into three disease groups: newly diagnosed (0–3 months), persistent ITP (3–12 months) and chronic ITP (>12 months) (Rodeghiero *et al*, 2009). The groups are loosely based on suspected outcome. For example, approximately 30% of adults will go into remission after a short period of thrombocytopenia with or without treatment. This usually occurs within the first 12 months. Fewer patients will go into remission after 12 months, and hence are defined as having chronic ITP (Rodeghiero *et al*, 2009). Although this is not well defined and other studies report 60% remission within 3 years of diagnosis (Sailer *et al*, 2006).

Treatment aims are different within these phases. Patients with newly diagnosed ITP may need urgent treatment to increase the platelet count, but irreversible treatment, such as splenectomy, should be avoided during this time. Steroid-sparing agents are needed for patients with persistent disease and, in patients with chronic disease, long-term safety aspects are most important. Patients with more severe disease may require more than one modality at a time.

Acute bleeding (Fig 2). Combinations of treatment are often needed in patients with acute bleeding, such as high dose IV methylprednisolone (500 mg to 1 g/day ×3) together with IVIG 1 g/kg on days 1 ± 2 (Boruchov *et al*, 2007; Provan *et al*, 2010). Tranexamic acid is a useful adjuvant, as is hormonal therapy for patients with significant vaginal haemorrhage. Platelet transfusions are also vital in life threatening bleeding (Spahr & Rodgers, 2008). We have used recombinant activated factor VII (rVIIa) in a patient with an intracranial bleed, but there are no controlled studies in this area. Similarly, we have also used TPO-RAs in combination with first line treatment in a patient with an intracranial bleed. TPO-RAs have been used in combination with other immunosuppression in acute disease; romiplostim $\pm$ rituximab (Contis *et al*, 2013) and eltrombopag with dexamethasone (Gómez-Almaguer *et al*, 2014), with good responses and these are likely to be used more frequently in this area (although this is not currently within the licensed use and needs more controlled studies).

Newly diagnosed (0–3 months) (Fig 2). For patients with newly diagnosed ITP (without life threatening bleeding) the guidelines and the consensus document recommend steroids or IVIG (Provan *et al*, 2010; Neunert *et al*, 2011). Steroid use includes oral prednisolone, IV methylprednisolone or oral dexamethasone. There is little evidence to guide what is

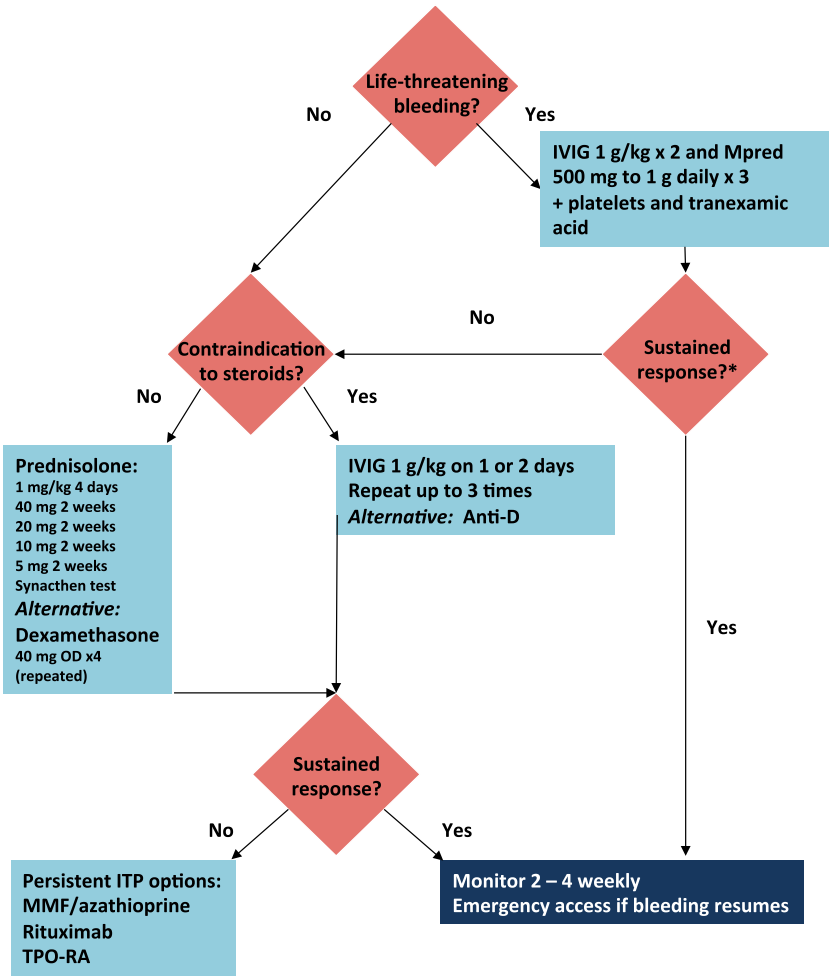

Fig 2. Management of patients with newly diagnosed immune thrombocytopenia, or recent relapse requiring treatment. In patients with acute bleeding, combination of intravenous (IV) methylprednisolone (Mpred) 500 mg to 1 g daily for 3 days together with intravenous immunoglobulin (IVIG) 1 g/kg on 1 or 2 days, together with supportive agents with tranexamic acid and platelets. In life threatening bleeding, use of rFVIIa and thrombopoietin receptor agonists (TPO-RAs) can be considered. For patients who do not have life threatening bleeds, but need treatment we use prednisolone 1 mg/kg daily for 4 days and then start a rapid tapering. Alternative treatments at this stage are repeated courses of dexamethasone 40 mg once daily (OD) for 4 days. In patients who have a contraindication to steroids, we use IVIG 1 g/kg on day 1 ± 2.

the 'best' steroid regime. A number of studies have suggested a higher complete response (CR) rate using high dose dexamethasone (Cheng *et al*, 2003; Mazzucconi *et al*, 2007; Wei *et al*, 2016). However dexamethasone is often poorly tolerated and comparative studies between dexamethasone and prednisolone are not consistent in their outcome. The ASH guidelines advocate a prolonged course of high dose oral steroids (Neunert *et al*, 2011), this is based on only one randomized controlled study (RCT) of continued prednisolone *versus* placebo after high dose methylprednisolone or IVIG where platelet counts were higher in the prednisolone arm (Godeau *et al*, 2002). However, outcome measures should not be restricted to the platelet count, but also take in to account the adverse effects of treatment, which is often considerable with the use of steroids.

Our aim is to use high dose steroids for as short a period as possible. As long as bleeding has stopped and the platelet count has stabilized (but not necessarily normalized), we use prednisolone 1 mg/kg for only 4 days and then reduce to 40 mg once a day (OD) for 2 weeks, 20 mg OD for 2 weeks, 10 mg OD for 2 weeks, 5 mg OD for 2 weeks then stop after performing a synacthen test (this is most relevant in patients who have been given a prolonged course of steroids). If the platelet count falls on tapering steroids, we use additional agents, such as IVIG, or add second line agents early on in the disease course. Some patients may need to stay on a

higher dose of steroids while second line agents are being started. In all patients on long-term steroids we give gastric and bone protection. Of note, using a shorter course of steroids does require more regular monitoring.

In patients who have a contraindication to steroids, or in patients where the diagnosis is not yet clear (and where the use of steroids may mask other underlying diseases) we use IVIG 1 g/kg on day one, repeated on day 2 if the response is not adequate. In patients who have an increased thrombotic risk and in the elderly who may not tolerate high doses of IVIG we use 0·4 g/kg × 5 days.

Anti-D remains a useful agent. It is especially useful for children and in human immunodeficiency virus (HIV)-related ITP, where it can give long lasting responses and is easier to use than IVIG (Cooper *et al*, 2002; Scaradavou *et al*, 2007). However, adverse effects have been reported after Anti-D, in particular intravascular haemolysis. Very rarely, this is associated with renal failure and fatalities – although the majority of patients in the case series had additional comorbidity (Gaines, 2005). The Food and Drink Administration have issued a black box warning for the use of Anti-D in ITP, recommending it should not be used in patients with anaemia or evidence of haemolysis and that urine should be monitored for the presence of free haemoglobin (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm203739.htm). In practice, the incidence of adverse effects is probably no different from the adverse effects from steroids or IVIG as long as it used correctly (Tarantino *et al*, 2007) and in conjunction with premedication with steroids e.g. 30 mg/kg of methylprednisolone (Despotovic *et al*, 2012).

Persistent ITP (Fig 3). The consensus document and the ASH guidelines list second line treatments in alphabetical order due to a lack of high-grade evidence. The three agents I use most commonly are: mycophenolate mofetil (MMF), rituximab and TPO-RAs. I have outlined the individual treatments in the next section. All are well tolerated with variable response rates. There is currently no good evidence to enable a decision between these options, or to guide which patients may be more likely to respond to each agent. The pros and cons of each are outlined in Table IV. A number of features influence our decision on treatment, including cost, availability of drugs, evaluation of potential triggers for ITP and the existence of additional co-morbidity, such as predisposition to infections, bleeding or thrombosis. Patient-specific factors also direct treatment. Currently in the UK, TPO-RAs are only funded in patients with chronic ITP (defined as 6 months in the RCTs).

Given these limitations, we have developed a guideline for management including the three commonly used treatments, which we adapt based on other patient factors (Fig 2B). If patients are at risk of infections, or have ITP secondary to infections, such as hepatitis or HIV, or secondary to immune dysregulation, such as post-transplantation, or related to immunodeficiency, such as common variable immunodeficiency (CVID), I recommend a TPO-RA (this is not a licensed indication and is not within National Institute for Clinical Excellence (NICE) guidance and requires specific application for funding in the UK). In patients with a normal immune system I start MMF 500 mg BD, increasing to 1 g BD if tolerated. Although there is less data for the use of MMF, we have found this a very useful agent in clinical practice. The advantage of MMF over rituximab is that if treatment fails, then MMF can be stopped and the immune system will return to normal, whereas with rituximab, B cells remain depleted for 6–12 months – the disadvantage is the time to response can be longer. If patients do not respond to MMF or have side effects to treatment, I consider other patient-related features (failure to respond is either continued bleeding needing further treatment or failure of platelet response within 8 weeks). For patients with co-existing autoimmune diseases, such as rheumatoid arthritis, where additional immunosuppression may be required, I use rituximab (although there is no evidence that rituximab is more effective in these patients). I also use rituximab in patients who have a thrombotic risk, and in those who require a more sustained increase in the platelet count (i.e. may require antiplatelet agents and may not be able to tolerate the fluctuating platelet counts seen with TPO-RAs). In patients with severe disease, I use a combination of rituximab and dexamethasone to increase the chances of response (see below in individual treatments for explanation).

In patients who do not need other immunosuppressive agents and if there is no thrombotic risk, my preference is TPO-RAs. The rational for using TPO-RAs early on in the disease process is that a proportion of patients will go in to a remission with TPO-RAs and may therefore avoid immunosuppression. In patients who have thrombotic risks and fail to respond to rituximab and dexamethasone, TPO-RAs can be used with caution (see below).

The majority of patients will respond to one of these agents. Decisions on timing of responses and decisions on when to move to a different agent depend on the degree of symptoms. In patients who are bleeding, more than one modality of treatment may be required.

Of important note, in women of childbearing age, I consider azathioprine as an alternative to MMF (see below for details).

Chronic ITP (Fig 4). Current options for patients with chronic ITP include continued use of MMF, azathioprine or TPO-RAs or repeated doses of rituximab (±dexamethasone). Alternative medications that also have some success in ITP include low dose prednisolone, dapsone (Zaja *et al*, 2012; Patel & Patil, 2015), danazol (Liu *et al*, 2016), vincristine (Stirnemann *et al*, 2016) and hydroxychloroquine (Khellaf *et al*, 2014a). We have little comparative data to understand which agents have the least toxicity with long term use.

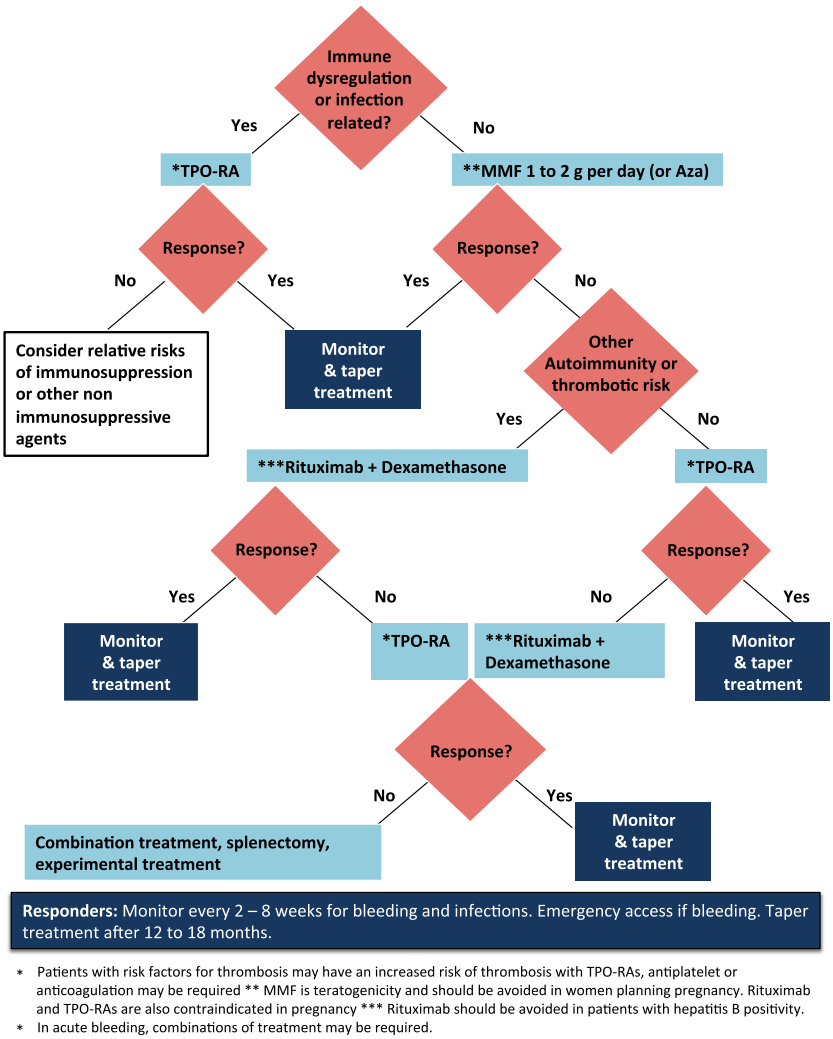

Fig 3. Treatment guideline for patients with persistent immune thrombocytopenia requiring treatment. In patients with an infective cause for Immune thrombocytopenia (ITP), or an underlying immune dysfunction (primary immune deficiency disorders, such as common variable immunodeficiency, chronic lymphocytic leukaemia or post-transplantation) we use thrombopoetin receptor agonists (TPO-RA). In patients with an otherwise normal immune system, we start mycophenolate mofetil (MMF). For women of childbearing age, I council against pregnancy or discuss alternatives, such as azathioprine (Aza). In patients who do not respond to MMF and have no thrombotic risks we start a TPO-RA. In patients who require other immunosuppressive agents, or who have a thrombotic risks, or if they cannot tolerate fluctuating platelet counts, we use rituximab (±dexamethasone weeks 1 and 3). In patients who have a complete response, treatment is tapered slowly and patients are continued on the lowest possible treatment dose.

There is also an argument to consider splenectomy at this time. It is still the intervention most likely to result in long term remissions and may allow avoidance of long-term medication and regular hospital visits (Ghanima *et al*, 2012). Better understanding of the long-term complications of each potential agent is needed to help guide treatment.

For all patients with chronic ITP, I run an annual panel of bloods including immunoglobulins, lymphocyte subsets, thyroid function tests and vitamin D levels during the winter months. For patients on rituximab and MMF, I repeat IgGs and lymphocyte subsets every 6 months. For patients on TPO-RAs we review the blood film on a regular basis (see below for more details).

Specific treatments

Mycophenolate mofetil (MMF). There are no RCTs of MMF in ITP. Retrospective studies show an approximate 50% response rate in adults with primary ITP, with poor responses in patients with virus-associated ITP (Taylor *et al*, 2015). We use a starting dose of 500 mg twice a day (BD) and increase to 1 g BD if tolerated. Side effects of treatment include headaches, gastrointestinal toxicity, liver function test (LFT) abnormalities and increased infections. This may be worse in older individuals. It can take 6–8 weeks for a sustained response. Some responding patients will be able to stop treatment after a number of years of treatment. In

Table IV. Pros and cons of second line therapies

	Advantages	Disadvantages
Mycophenolate mofetil	Tablet, no food restrictions Good short term tolerability Low relative cost Immune system returns to normal on stopping treatment Approximate 50% response rates	Unclear long term toxicity (including secondary malignancies) Increased infections, lessens effectiveness of OCP Cannot be used in pregnancy (known teratogenicity) Delayed responses (4 to 8 weeks)
Rituximab	Responses last for >9 months 20–30% long term (>5 year) responses Higher long term response rates (70%) in women in the first 24 months od ITP	No response in 40% of patients No predictors of response and frequent relapses Hypogammaglobulinaemia in small number of patients Reduced vaccine responses Very rare incidence of PML Reactivation of hepatitis B
Thrombopoietin receptor agonists(eltrombopag and romiplostim)	Not immunosuppressive Possible long term cures (20–30%)	Possible increased thrombosis risk Potential for long term bone marrow changes Long term safety data (>10 years) in only a few hundred patients Fluctuating platelet counts can be difficult to manage
Splenectomy	60% life long remissions Avoid long term medication and hospital visits	Life long increased risk of septic shock Life long increased risk of thrombosis 40% failure rate and poor predictors of outcome

ITP, immune thrombocytopenia; OCP, oral contraceptives; PML, progressive multifocal leucoencephalopathy.

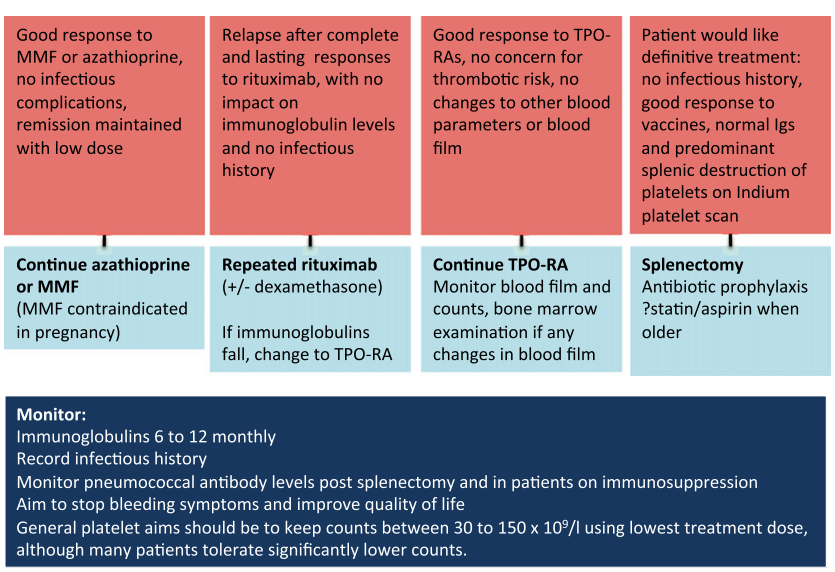

Fig 4. Management of chronic immune thrombocytopenia. For patients who do not go into remission within 12 months, long-term toxicities of treatment should be considered. For patients who would like definitive treatment and to stop medications, and who are not considered to have infectious risks, splenectomy may be the right treatment choice. For patients who have stablised on a low dose of immunosuppression without increase in infections, this may be continued. For patients who respond well to rituximab, but relapse, further treatment can be used (with the caveat that a proportion of patients on repeated rituximab may develop hypogammaglobulinaemia). Patients who have responded to TPO-RAs but are not able to come off treatment can continue on these agents, with monitoring of the blood parameters and blood film. For all patients, I measure immunoglobulin and pneumococcal antibody titres every 6–12 months. MMF, mycophenolate mofetil; TPO-RAs, Thrombopoietin receptor agonists.

patients who have achieved a complete remission for more than 12 months, I gradually reduce MMF over a period of months. For patients who require long-term use, monitoring other parameters, such as mean cell volume (MCV) change or neutropenia is important because of the potential bone marrow effects. I also monitor immunoglobulin levels in all

patients on immunosuppression. ITP is associated with CVID in a small proportion of patients with ITP, which may develop many years after the diagnosis of ITP (Michel *et al*, 2004; Knight & Cunningham-Rundles, 2006).

There is no direct comparison between azathioprine and MMF. In our experience, MMF is better tolerated and has a higher chance of response. However, MMF has significant teratogenicity – with 21–27% of pregnancies developing fetal abnormalities (www.toxbase.org) – and must be avoided in pregnancy. In contrast, azathioprine is safe during pregnancy; this may therefore be a better treatment for women of childbearing age.

The long-term risks of immunosuppression must also be considered. Data describing increased risk of secondary malignancies in patients on immunosuppression arises mostly from literature involving patients who have undergone organ transplantation, where the immunosuppressive burden is much higher. It is not known what the risks are for patients on MMF or azathioprine for ITP. For many patients only short-term use is required. Maintaining the lowest possible dose and educating patients on other risk factors, such as smoking, sun exposure and monitoring of moles are important.

Rituximab. Rituximab is useful in patients who have not responded to steroids, or who require high doses of steroids to maintain a 'safe' platelet count. It is also useful in those not tolerant of other agents and can keep patients well and out of hospital for at least a year (Arnold *et al*, 2012; Khellaf *et al*, 2014b). However, only 50 to 60% of patients respond to treatment and most patients will relapse and require further treatment (Patel *et al*, 2012; Ghanima *et al*, 2015). Repeated B cell depletion can cause reduced vaccine responses (Nazi *et al*, 2013) and severe hypogammaglobulinaemia (Cooper *et al*, 2009; Levy *et al*, 2014), although the latter appears to be uncommon (Aguiar *et al*, 2016). This is particularly relevant in children and if splenectomy is considered at a later date. If patients are hepatitis B surface antigen or antibody positive (not related to vaccination or IVIG therapy), ideally rituximab should be avoided. The immunosuppressive effects of rituximab may be worse in those given concomitant immunosuppressive agents, or those with existing immunodeficiency; testing of immunoglobulin levels pre treatment is recommended (Kado *et al*, 2016). Progressive multifocal leucoencephalopathy has been described after rituximab, but this is more common in patients with rheumatological or lymphoproliferative disorders with an estimated incidence of 1 in 25 000 individuals (Clifford *et al*, 2011). It is exceptionally rare in patients with ITP (Carson *et al*, 2009) and more commonly associated with the additional use of alkylating agents.

Although the most recent RCT of rituximab *versus* placebo showed no difference in the 18 months outcome between the two arms, further analysis of this data shows a small number of patients within the first 6–12 months of diagnosis appear to have benefit and up to 30% of patients may maintain a long term remission/cure (Ghanima *et al*, 2015). There are also preliminary reports of long-term responses (up to 70%) in women within 24 months of diagnosis (Bussel *et al*, 2014, 2016) and other studies suggesting a 70% CR rate at 2 years in newly diagnosed patients receiving combinations of dexamethasone, low dose rituximab and ciclosporin (Choi *et al*, 2015). Results from these studies may change our management and highlight the real need for further comparator studies.

Dose of rituximab—A number of different doses have been used. All appear to show responses, but standard doses such as 375 mg/m^2 weekly for 4 weeks, or 1 g twice (as used in rheumatology) may result in both a higher response rate and a longer duration of response (Mahévas *et al*, 2013) – we use 500 mg weekly for 4 weeks.

Studies have also shown increased response rates when combined with dexamethasone (Zaja *et al*, 2010; Bussel *et al*, 2014) and patients who do not respond to rituximab alone may respond to the combination. I tend to use this combination in patients who need a rapid increase in their platelet count.

Larger RCTs are in development to establish which patients are most likely to go in to long-term remissions with rituximab and what regime gives the best response. Long-term studies are required to assess whether use of rituximab causes persistent B cell depletion or reduced responses to vaccines.

Thrombopoietin receptor agonists (TPO-RAs). Romiplostim and eltrombopag have transformed the care of patients with chronic refractory ITP. They have shown good efficacy in both splenectomised and non-splenectomised patients in large RCTs (Kuter *et al*, 2008, 2010, 2013; Cheng *et al*, 2011; Saleh *et al*, 2013). They are licensed for use in adults with refractory ITP.

NICE guidance for the agents are the same: "eltrombopag and romiplostim are recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if: their condition is refractory to standard active treatments and rescue therapies, or they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies."

The European Medicines Agency (EMA) recently revised their recommendations and do not now require splenectomy before use of romiplostim or eltrombopag.

There are no comparative studies of these agents and both show good responses both pre- and post-splenectomy and good interim safety profile (Saleh *et al*, 2013; Bussel *et al*, 2015; Cines *et al*, 2015). The major difference is the route of

administration. Romiplostim is given as a subcutaneous injection once a week whereas eltrombopag is given as a daily tablet with dietary restrictions (no calcium containing products 4 h before and 2 h after treatment).

Special features of TPO-RAs

Starting doses—The median dose required to sustain a response in the RCTs of romiplostim was 3 μg/kg. Many physicians therefore start romiplostim at 2–3 μg/kg rather than the 1 μg/kg recommended in the product license; we often round up to one vial depending on the patients' weight.

Eltrombopag is usually started at 50 mg OD and titrated up or down according to platelet count (patients of Asian origin should be started on 25 mg). Higher doses of eltrombopag have been used in patients with aplastic anaemia, (Olnes *et al*, 2012) but it is not yet clear whether this is useful in ITP (and is not within the license).

The time to treatment response is variable between patients. I monitor for changes in bleeding symptoms and general health. Patience and small changes in doses are required when using these agents. Although the standard guidance is to stop treatment after 6 weeks if there is no response, some patients have intermittent responses initially and take longer than 6 weeks for a sustainable response. If patients are no longer symptomatic (i.e. not bleeding) then the frequency between counts can be extended. I tend to review patients who are stable between 4 and 8 weekly to include FBC and LFT monitoring. Patients have an emergency access card for if they experience bleeding or other symptoms between visits.

Managing fluctuations in counts—Almost all patients have fluctuations in their platelet count. The aim of treatment is not to maintain a normal platelet count, but rather a platelet count within a 'safe range'. I aim for platelet counts between 30 and 250 $\times$ 10^9/l. In some patients fluctuations are very difficult to manage. Addition of a second agent, such as steroids or MMF, can help in some patients. In others, changing the TPO-RAs may be useful. Both agents can cause fluctuations in counts, although the fluctuations appear to be less severe with eltrombopag. Other methods are to reduce to minimal doses such as 1 μg/kg of romiplostim, or alternate days of 25 mg eltrombopag together with immunosuppression, such as MMF, ciclosporin, steroids or IVIG. IVIG responses are often markedly higher after a TPO-RA is started.

Switching TPO-RAs—Changing TPO-RA can be helpful in both directions, either due to poor responses, large fluctuations in platelet responses or because of problems with route of administration (Khellaf *et al*, 2013; Kuter *et al*, 2015). There is no clear data on how to switch agents, but this depends on the reasons for switching and the individual platelet counts.

Use of both agents—Romiplostim and eltrombopag have different methods of activating the thrombopoietin receptor and may have different biological effects. Combining treatments has been successful in very refractory patients (Kuter *et al*, 2015).

Stopping TPO-RAs—For some patients, their requirement for TPO-RAs decreases over time and up to 30% of patients go in to a long-term remission off treatment, 1–2 years after starting treatment and after 10–15 years of chronic ITP (Ghadaki *et al*, 2013; Mahévas *et al*, 2014; Bussel *et al*, 2016). The long-term remissions seen in patients who have previously been refractory to treatment make these agents particularly appealing, especially if only a short period of use is required. I slowly reduce the TPO-RAs in patients who have achieved a normal platelet count. In practice, those who do go in to remission tend to have a steady rise in their platelet count, requiring reduction in the dose anyway.

Potential adverse effects. i) Bone marrow stimulation—Increased reticulin deposition has been reported in patients on TPO-RAs and occasional leukoerythroblastic picture has been described although these features resolve on stopping treatment. Prospective studies have not suggested any long-term adverse effects so far (Bussel *et al*, 2009; Kuter *et al*, 2009; Ghanima *et al*, 2011, 2014; Boiocchi *et al*, 2012). Cytogenetic changes have been described in patients with aplastic anaemia; this does therefore need continued vigilance – although it is more likely to reflect the progression of aplastic anaemia rather than the treatment (Desmond *et al*, 2014). I currently recommend a bone marrow before starting treatment, although this is not standard practice, and review the blood film regularly together with the MCV. If there are any changes on film or blood parameters, I repeat the bone marrow.

ii) Possible increased risk of thromboembolism—In the RCTs of both eltrombopag and romiplostim there was a surprisingly high incidence of thromboembolic events (TEs). These occurred on both the treatment arm and the placebo arm. They also occurred at a variety of platelet counts (often below normal platelet counts). Patients with ITP appear to have an increased risk of venous thromboembolism (VTE) (Sarpatwari *et al*, 2010a) and it is unclear whether TPO-RAs were causative in these cases. A more recent metanalysis of all studies does suggest an increased risk of TE on these agents (Catalá-López *et al*, 2015). Patients who developed TEs on study had other risk factors for thrombosis. Given this potential association, I have been cautious about using these agents in individuals who have cardiac history, particularly in patients with cardiac stents. However, managing ITP is a balance of risks, and patients with very difficult ITP who also have a cardiac history may require TPO-RAs in order to keep their platelet counts at a safe level in order to take antiplatelet agents or anticoagulation.

Splenectomy. Splenectomy is still the management strategy most likely to render long-term remission and may allow avoidance of long-term medical treatments. There are both short and long term risks of splenectomy (Rodeghiero & Ruggeri, 2012). There is a well-described small risk of overwhelming septic shock. Continued use of penicillin prophylaxis and regular vaccination against encapsulated organisms is important in long term care and may be forgotten in those in long-term remission. More recently there has been concern about an increased risk of VTE and pulmonary hypertension (Boyle *et al*, 2013). An oral presentation at ASH 2014 described a case controlled study comparing 70 patients with ITP and splenectomy more than 10 years previously to case control ITP patients who had not undergone splenectomy (Thai *et al*, 2014). The authors described an increased cumulative incidence of VTE in the splenectomy group, increased cardiovascular disease (13% in the splenectomy cohort compared to 2·8% in the non splenectomised cohort); increased transient ischaemic attacks (TIAs) (6 in splenectomised cohort *versus* none in the non splenectomised cohort) and increased serious infections (5 septic shock with 3 deaths in splenectomised patients *versus* none in the non splenectomised group). Although the authors continue to use splenectomy as second line treatment, they suggest monitoring for vascular risk factors and the potential for using statins (Thai *et al*, 2014).

In patients considering splenectomy, I refer them for an indium-labelled -platelet sequestration scan. Patients with predominant splenic sequestration appear to have better responses (approximately 90%), compared to patients with mixed liver and spleen destruction who have a 40% chance of remission (Sarpatwari *et al*, 2010b; Palandri *et al*, 2014).

Refractory disease. The management of patients who do not respond to standard treatment can be very challenging. These patients have significant morbidity and mortality (Mahévas *et al*, 2016). There is an absence of data in this area (Cuker & Neunert, 2016). Re-evaluation of the diagnosis is important at this stage.

Given that increasing experimental data suggest that ITP may be caused by cytotoxic T cell disease and/or antibody-mediated disease, and that both platelet destruction and platelet production may be effected in ITP, combinations of treatment may be beneficial (Boruchov *et al*, 2007; Choi *et al*, 2015). Combining immunosuppressive treatments with TPO-RAs show the most promise (Mahévas *et al*, 2016). Additional immunosuppressive agents can be useful, including cyclophosphamide (Verlin *et al*, 1976; Reiner *et al*, 1995), rapamycin (Li *et al*, 2013), and anti-TNF agents (McMinn *et al*, 2003; Litton, 2008). However some patients remain refractory to all medications, intermittently using IVIG and steroids for acute episodes. Novel targets include: the spleen tyrosine kinase (Syk) inhibitor fostamatinib, which has shown promise for refractory patients (8 of 16 patients responded to treatment) (Podolanczuk *et al*, 2009) and is in phase 3 trials. Other agents targeting T cell co-stimulation – toralizumab (IDEC-151) (Kuwana *et al*, 2004) and ruplizumab (hu5c8) (Patel *et al*, 2008), or FcR binding and signalling – GMA161 (Flaherty *et al*, 2012) are in study. Newer TPO-RAs are also in trial – avatrombopag, 23A11 and amifostine. A summary is described in Shih *et al* (2014).

Other aspects of ITP

ITP in childhood. The management of ITP in childhood is variable between countries (Cooper, 2014). The UK guidelines recommend that children do not need treatment unless they are bleeding (Grainger *et al*, 2012). This has resulted in fewer children being treated with prolonged steroids and has been very successful for children who have acute ITP with no bleeding or bruising and go in to a quick remission. However, some children do have significant bruising and bleeding, which can have can have an impact on their health-related quality of life, with reduction in school and sport participation. For these children, treatment can have a positive impact. Internationally, many centres continue to treat children routinely at platelet counts less than 20×10^9/l.

Treatment options for children are similar to adults. There is very little data for the use of MMF in children and it is not recommended in either guideline. However it has been used in children with other autoimmune diseases and we have used it in ITP with good success at relatively low doses. Rituximab may have a use for children who have severe acute disease who are not responsive to steroids or requiring high dose of steroids (Cooper & Bussel, 2010; Liang *et al*, 2012). However due to its B cell depletion effects I do not use repeated doses of rituximab in children unless the risk of not treating is considered to be very high. Splenectomy has a good safety and efficacy profile in children with ITP (Kühne *et al*, 2007). However the long-term data from adult studies shows this should be used with caution.

So far, both eltrombopag and romiplostim have shown good efficacy and tolerability in children with ITP. Higher doses appear to be required in children (Bussel *et al*, 2009; Grainger *et al*, 2015; Tarantino *et al*, 2016). For most children the duration of treatment may be only a few years, further reducing the toxicity of treatment while improving quality of life. If a proportion of children can go in to remission with these agents, and without the immunosuppression of other agents, these could become the treatment of choice for children with persistent and chronic ITP. RCTs in early disease are needed.

Discussion

The management of ITP has dramatically improved over the last 50 years. The development of a terms and definitions document by the international ITP group has helped with establishing the diagnosis and stages of disease, which helps

to define and compare study outcome data. The development of new treatments with safer IVIG products, use of IV Anti-D, rituximab and TPO-RAs has reduced the requirement for steroids and splenectomy. Given that the most common cause of morbidity and mortality are related to infectious complications from steroids and splenectomy, this has significantly improved management.

However, many limitations remain. Poor understanding of the pathology of the disease in individual patients and the lack of a diagnostic test or biomarkers to track disease activity results in frequent treatment failures and unnecessary treatment toxicity. The limited comparative studies in this area mean there is little evidence base for different treatment options. This restricts physician decision-making and is frustrating for patients, particularly when treatments fail.

There is an unmet clinical need for further research in this area: basic science research is needed to help identify the cause of ITP and allow more targeted treatments together with national/international comparative studies for first and second line treatments. The end points for studies should include long-term remission rates, HRQoL studies as well as assessment of toxicities, including TEs, bleeding, infection and other secondary diseases. There are also some patients who remain refractory to standard medications. These patients have significant burden of disease with high morbidity and mortality and need novel, targeted therapy, based on basic science research and in collaboration with pharmaceutical partners.

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