Should medical treatment options be exhausted before splenectomy is performed in adult ITP patients? A debate

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Editorial Manager(tm) for Annals of Hematology
Manuscript Draft

Manuscript Number: AOHE-D-10-00296

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Article Type: Review Article

Keywords: Immune Thrombocytopenia; Splenectomy; Thrombopoietin Agonists; Corticosteroids

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The decision whether to proceed to splenectomy or try other medical therapies in corticosteroid-refractory patients remains patient-specific. Splenectomy has its risks (including perioperative and long-term risks), and relapse/nonresponse are relatively common, but it offers the possibility of cure in the majority of patients. However, newer treatments may potentially allow splenectomy to be deferred for prolonged periods, as well as providing alternative treatment options for patients who fail splenectomy.

REVIEW ARTICLE **[26 MAY 2010]**

Should Medical Treatment Options be Exhausted before Splenectomy is Performed in Adult ITP Patients? A Debate

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Target Journal: Annals of Hematology

Abstract

Patients with primary immune thrombocytopenia (ITP) may require treatment to reduce the risk of serious bleeding if platelets remain consistently below 30 x 10^9/L. While approximately 70-80% of patients respond to an initial course of corticosteroids, relapse is common. For steroid-refractory patients, there is a choice between surgical splenectomy and further medical treatments, based on many factors including the patient's bleeding history, fitness for surgery, comorbidities, tolerance of adverse events, lifestyle and preferences. Treatments that have traditionally been used (corticosteroids, azathioprine, danazol) suppress the immune system, potentially predisposing patients to infection. Recent insights into the underlying pathophysiology of the disease have allowed the development of targeted therapies, including the thrombopoietin (TPO) receptor agonists, which enhance platelet production. Phase III trials have found romiplostim and eltrombopag to be well tolerated and effective in elevating platelet counts and reducing bleeding in both splenectomised and nonsplenectomised patients with chronic ITP. The B-cell targeted monoclonal antibody rituximab has also shown some potential in this setting, although data are currently limited and there are toxicity concerns.

The decision whether to proceed to splenectomy or try other medical therapies in corticosteroid-refractory patients remains patient-specific. Splenectomy has its risks (including perioperative and long-term risks), and relapse/nonresponse are relatively common, but it offers the possibility of cure in the majority of patients. However, newer treatments may potentially allow splenectomy to be deferred for prolonged periods, as well as providing alternative treatment options for patients who fail splenectomy.

Keywords: Immune Thrombocytopenia; Splenectomy; Thrombopoietin Agonists; Corticosteroids

INTRODUCTION

Primary immune thrombocytopenia (ITP; previously referred to as idiopathic thrombocytopenic purpura), is defined as isolated thrombocytopenia (platelet counts ($<100 \times 10^9$/L) of unknown cause. Clinical manifestations vary and may be absent or range from petechiae or purpura and easy bruising to potentially life-threatening bleeding episodes. Whereas ITP in children is often characterised by abrupt onset of petechiae and purpura, associated with viral infection or immunisation, and short-lived (<6 months), ITP in adults typically has a more insidious onset and is more likely to follow a chronic course (≥12 months).

The severity of thrombocytopenia is the most important risk factor for major bleeding and management of chronic ITP is aimed at preventing bleeding, rather than normalising the platelet count. Treatment is usually indicated in patients with platelet counts $<30 \times 10^9$/L and those with counts between 30 and 50×10^9/L with bleeding or at risk of bleeding (e.g planned surgery, dental extraction, parturition, active peptic ulcer) [1, 2]. Corticosteroids are the standard first-line treatment, while intravenous immune globulin (IVIg) and anti-D (with or without methylprednisolone and platelet transfusions) are used mainly for 'rescue' treatment of serious bleeding episodes. Anti-D has also been an option for nonsplenectomised Rhesus-positive patients who are unable to receive corticosteroids, but is no longer available in the EU. Typically, a course of prednis(ol)one is given, at a dosage of 1 to 2 mg/kg/day, with dosage being tapered after a short time (usually within a few weeks), in order to avoid inducing corticosteroid-related adverse effects. Another regimen used in many countries is 1-4 courses of dexamethasone 40 mg/day for 4 consecutive days, at 14-day intervals [3].

Approximately 70-80% of patients respond to corticosteroids initially [3], but relapse is common with many patients requiring repeated or prolonged treatment. For second-line treatment, there is a choice between surgical splenectomy (in patients who are fit for surgery) and a wide range of medical treatments (**Figure 1**). While international guidelines for ITP have been published [1-3], there is no consensus regarding the best sequence of treatments and treatment is individualised, based on such factors as the patient's bleeding history, comorbidities, tolerance of adverse events, degree of worry about disease burden, lifestyle, accessibility to care, and preferences. For reviews on the subject, see Bussell [4], and Cines and McMillan [5].

As the choice of treatments has expanded in recent years with the introduction of several new agents, this article examines the question of whether medical treatment options should generally be exhausted before splenectomy is performed in adults with chronic severe ITP requiring treatment. Arguments for and against early splenectomy are presented.

ARGUMENTS AGAINST EARLY SPLENECTOMY

1. The natural history of adult ITP varies and spontaneous remissions can occur

Chronic ITP in adults has a variable and unpredictable course, with very wide inter-patient heterogeneity. Spontaneous remissions (without splenectomy) occur in approximately 10% of patients, with and without medical treatment. There is increasing evidence that remissions can occur up to 1 or 2 years after onset [6, 7], suggesting that surgery may be deferred for prolonged periods [3, 7, 8]. For instance Sailer et al. found that in 114 patients with platelet count < 20 x 10^9/L at diagnosis who were treated with first-line therapies (corticosteroids and/or IVIg), complete or partial remission was most likely to occur within the first 6 months (28 [30%] and 15 [13%] patients), but a further 17 complete and 8 partial responses occurred between 6 months and 3 years [7]. Thus, approximately 60% of patients eventually achieved remission, supporting the argument for delaying definitive decisions in ITP.

2. Splenectomy results are unpredictable and it is associated with significant morbidity

Splenectomy has been utilised for treatment of 'idiopathic purpura' since the early 1900s [9], when there was no rigorous testing of procedures. This procedure is associated with a number of risks, including complications of general anaesthesia and bleeding (the major immediate risk for an ITP patient), as well as perioperative complications such as pneumonia, wound/other infection, ileus, and thrombosis. Complication rates vary considerably [10-13] and appear to be higher in those aged ≥60 years [14]. Laparoscopic splenectomy is associated with lower complication and mortality rates than open splenectomy [10, 15] (9.6 *vs* 12.9% and 0.2% *vs* 1%) [10], but is nevertheless associated with the risk of infectious complications. Moreover, follow-up times are much shorter and complications associated with surgery in general are still apparent. Overwhelming post-splenectomy infection (OPSI) is the

major concern after splenectomy, although quantifying the risk is difficult because of the lack of consistent data. Other long-term complications include vascular events (**Table 1),** as recently reviewed by Crary and Buchanan [16].

Approximately one-third of patients fail to achieve complete response to splenectomy and a substantial proportion of initial responders subsequently relapse [10, 12] (Figure 2). Although most relapses occur within the first 2 years after splenectomy, relapses continue to occur after that time point [12, 17] and it has been suggested that most patients eventually relapse [18]. There is at present no widely accepted and reliable test to identify patients who will fail splenectomy. It is unclear whether indium-labelled autologous platelet scanning [19] or response to high-dose IVIg [20, 21] can accurately predict response. Moreover, platelet scanning is expensive and not yet widely available and results may be poor at very low platelet counts.

3. Splenectomy is an irreversible procedure that limits subsequent treatment options

As there is no current work on preservation of spleen tissue and later reimplantation, splenectomy is at present an irreversible procedure [22]. Patients who do not respond to splenectomy may not respond to many of the currently available immunosuppressive treatments [23] and are ineligible for anti-D therapy [22], thus their subsequent treatment options are very limited. These patients have a poor prognosis: a 12-year follow-up of >100 patients who failed splenectomy found that almost 30% responded poorly to subsequent treatments. 30% of patients died: 16% from ITP-related causes (bleeding 10% or complications of treatment, including sepsis 6%) [**Figure 3**] [24]. A study by George et al. also indicated that patients who fail splenectomy have worse health-related quality of life (HRQoL) compared with non-splenectomised patients who have similar platelet counts [25]. This was shown by lower scores for 7 of 10 scales of the disease-specific ITP-PAQ (ITP Patient Assessment Questionnaire) instrument: Symptoms, Bother, Activity, Social Activity, Fear, Psychological Health and overall quality of life.

Moreover, splenectomised patients are immunocompromised and therefore at risk of fatal bacterial infection, requiring lifelong continuing vigilance. Patients are generally immunised with pneumococcal, *Haemophilus influenzae* and meningococcal

vaccinations at least 2 weeks before surgery, with revaccination according to local practices. Vaccinations may not be effective in patients who have received rituximab in the previous 6 months [3]. Vaccination against influenza is also recommended by some authorities [26]. Antibiotic prophylaxis is required after surgery, with British authorities suggesting that this should be continued for several years [1], or lifelong [26, 27]. However, this practice is not based on strong evidence and is not actually incorporated in guidelines from other countries [2]. Surveys have shown a need for better education of patients regarding the risk of post-splenectomy infection [28].

Finally, splenectomy is increasingly seen as 'removal of a healthy organ' and many well-informed patients refuse splenectomy on this basis. This is reflected in the falling rates of splenectomy over recent years, as new treatments become available [29].

4. New agents have changed the treatment paradigm.

Increased understanding of the pathophysiology underlying ITP has allowed the development of many new treatments. While conventional therapies such as corticosteroids and splenectomy primarily focus on reducing platelet destruction [30, 31], the finding that platelet production is suboptimal in a substantial proportion of patients with ITP [32, 33] has led to development of the TPO mimetics, which enhance platelet production and may therefore provide better outcomes [34]. Additionally, increased knowledge regarding the peripheral role of B-cells in autoimmune disease has led to evaluation of agents that target these cells [35].

TPO mimetics

The identification of thrombopoietin (TPO) in the mid-1990s as the primary growth factor that regulates platelet production paved the way for development of a new class of agents, the TPO receptor agonists [36]. The 'peptibody' romiplostim [37-39] was the first TPO mimetic to reach the clinic. Unlike the earlier recombinant TPOs [40, 41], romiplostim does not cross-react with endogenous human TPO, since its active peptide domain does not share any sequence homology with native TPO [37, 42]. It is administered as a weekly subcutaneous injection, at a starting dose of 1 mcg/kg, which is individualised according to patient response.

Data from two parallel Phase III trials in patients with severe and refractory chronic ITP indicated that treatment with romiplostim results in a platelet count of ≥50 x 10^9/L in approximately 80% of patients. Eighty-eight percent of non-splenectomised and 79% of splenectomised patients achieved the target range of 50-200 x 10^9/L for at least 4 weeks (**Figure 4)** [34]. Platelet increases are observed within 1-2 weeks of starting treatment, with approximately 50% of patients achieving platelet counts ≥50 x 10^9/L within 2-3 weeks. Bleeding events are significantly reduced and the majority of patients are able to reduce or discontinue concurrent ITP therapy including steroids, azathioprine and danazol, as well as requiring less rescue medication (IVIG, and Anti-D) [**Figure 4]** [34]. An open-label extension study has demonstrated the long-term efficacy and tolerability of romiplostim in 142 patients treated for periods of up to 3 years [43]. Platelet responses (≥50 x 10^9/L and double the baseline value, in the absence of rescue medication within the preceding 8 weeks) were seen in 87% of patients. Many patients (~60%) were able to self-administer their romiplostim injections. A 5-year update was recently presented at the 2009 ASH Annual Meeting , in which it was shown that patients were able to maintain platelet counts within the target range with minimal dose adjustments and that adverse events did not increase over time [44]. Romiplostim has also been reported to improve HRQoL in chronic ITP patients [25].

Adverse events were reported in almost all patients in the pivotal phase III romiplostim studies (romiplostim 100%, placebo 95%), but were generally mild to moderate and appeared to be related to the underlying disease [34]. Very few patients receiving long-term romiplostim treatment discontinue the drug because of adverse events [34, 43]. There was no evidence of increased risk of thromboembolic events [34, 45] and no evidence of antibodies that cross-reacted with endogenous TPO or affected the platelet response [34, 43], except in one instance, where a patient transiently developed romiplostim-neutralizing antibodies. In two patients neutralizing antibodies to romiplostim were detected which did not cross-react with endogenous TPO. There is a risk of rebound thrombocytopenia after stopping treatment and patients who discontinue romiplostim should be carefully monitored. Presence of/increased bone marrow reticulin has been found in a number of patients treated with various TPO mimetics [34, 43, 46]. The clinical significance of these findings is yet to be clarified, although reticulin deposition is often present in the bone

marrow of individuals with and without ITP and there has been no evidence of progression to collagen fibrosis, or clonal myeloproliferative disorder after romiplostim treatment (**Table 1**).

Other TPO mimetics recently developed include the synthetic small molecule agent eltrombopag [47, 48]. It is given as an oral once-daily dose, on an empty stomach (separated from divalent cation-containing foods and supplements by at least 4 hours) [49]. Phase III data (n=114 patients) have been published [50]. Eltrombopag (initial dose 50 mg/day) achieved platelet counts of $\geq 50 \times 10^9$/L on day 43 in 59% of patients, while decreasing bleeding symptoms. Adverse events were reported in 59% of eltrombopag and 37% of placebo recipients. Hepatobiliary laboratory abnormalities were more common with eltrombopag than with placebo and cataracts were reported with similar frequency in both treatment groups [50]. Longer-term data from a phase III extension study [51] and a 6-month phase III study [52] appear to support these findings but are yet to be fully published in the literature.

Rituximab

The anti-CD20 antibody rituximab, which selectively depletes B-cell lymphocytes, is licensed for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis [53] and has been used extensively off-label for treating a range of autoimmune diseases, including ITP[54]. The optimal dose and timing of rituximab in chronic ITP are yet to be defined and dosage schedules in most studies have been based on those used in the lymphoma setting, i.e weekly doses of 375mg/m^2 for 4 weeks.

An analysis of data from descriptive and comparative studies suggests that rituximab produces a 63% overall response rate (46% complete response rate; >150 $x10^9$/L) in patients with chronic ITP, although the definition of response varied widely in the reported trials [54]. The median time to response was 5.5 weeks from the first dose and median duration of response 10.5 (range 3.0-20.0) months. Retreatment with rituximab was successful in inducing repeat responses in relapsed complete responders [55]. Phase III data from the first-line setting (n=103 patients) have recently been reported: a combination of rituximab and dexamethasone achieved a response rate of 63%, versus 36% for dexamethasone alone (P = 0.004). This

combination provided an effective salvage therapy for 56% of patients who were refractory to dexamethasone [56].

Toxicities of rituximab include infusion reactions (headache, fever, chills, hypotension, bronchospasm), particularly with the first dose, severe mucocutaneous reactions, risk of hepatitis B reactivation and Progressive Multifocal Leukoencephalopathy (PML) [53] (**Table 1**). The overall risk of fatal adverse events is estimated at 2.9% [54]. PML, while rare, has an extremely high mortality rate of 90% [57]. Concern regarding such events has led to warnings on the FDA[58] and EMEA [53] labelling. However, it is important to note that many of these events have occurred in heavily immunosuppressed lymphoma patients who were receiving other treatments.

A low-dose rituximab regimen (100mg weekly for 4 consecutive weeks) has been explored in ITP patients, with encouraging results [59, 60]. In one small series sustained complete response was achieved in four of 7 patients (57%) and no infusion reactions were seen [59]. In a slightly larger series overall and complete responses were achieved in 21/28 (75%) and 12/28 (43%) patients respectively [60]. Further studies are warranted to confirm these preliminary data, as a lower dose may be associated with a lower risk of toxicities.

Other targeted agents under development

Other targeted agents are being developed for ITP and these may expand the list of treatment options in the future. As well as additional TPO receptor agonists and B-cell-depleting agents, other approaches that are being studied include Syk kinase inhibitors [61], targeting of co-stimulatory signal (e.g the CD80/CD86 inhibitor CTLA-4-Ig [Abatacept]), B-cell survival signal, regulatory T-cells and macrophage FcγR function (reviewed by Li and Hou [62]).

ARGUMENTS FOR EARLY SPLENECTOMY

1. We have a century of history and experience with splenectomy

Splenectomy has been utilised to treat ‘idiopathic purpura’ since the early 1900s [9] and remained the ‘first-line, gold standard procedure’ until the 1950s, when steroids

were introduced [63]. While many additional medical therapies have since emerged, splenectomy remains the second-line treatment of choice for many physicians treating ITP.

2. Splenectomy provides durable long-term responses for most patients and responses can be predicted

No other treatment has the overall success rate of splenectomy, with approximately two-thirds of patients achieving durable complete response [10, 17]. Vianelli et al. estimated a >70% probability of maintaining response for 5 years after surgery, based on their follow-up of 402 splenectomised patients [17].

^{111}Indium-labelled autologous platelet scanning may provide a sensitive predictor of response [19, 64]. Among patients shown to have splenic platelet destruction, approximately 90% will respond to splenectomy, while a similar proportion of those with hepatic or diffuse platelet destruction fail splenectomy [19]. A good response to IVIg may predict a favourable response to splenectomy [20], as may younger age; higher peak platelet count at splenectomy and having received ≤1 previous therapy (all $P<0.0001$ by univariate analysis) [17].

3. The safety profile of splenectomy is acceptable: immediate risks are known and can be minimised

Several advances in surgical practice over the years have led to a significant decrease in mortality and complication rates associated with splenectomy [10]. Predniso(lo)ne or IVIg can be given to raise the platelet count prior to surgery and thus reduce the risk of bleeding [2]. Laparoscopic splenectomy, introduced in 1991, has been associated with less blood loss, more rapid recovery and lower complication and mortality rate than open splenectomy [10, 15]. Preoperative vaccination and postoperative antibiotics have led to declining rates of fatal sepsis. Indeed, cases that have been reported occurred prior to the introduction of pneumococcal vaccination [2]. Results of two analyses (n = 402 and 208 patients, respectively) found that no cases of fatal sepsis have occurred in Italy [6, 17]. Overall, the risk of septicaemia following splenectomy may be less than the risk of intracranial haemorrhage in a nonsplenectomised ITP patient.

4. Currently available medical treatments have limitations

In general, treatments used for ITP have considerable adverse effects, as summarised in **Table 1**. Elderly patients and those with comorbid conditions may be at greater risk.

Only a minority of patients with ITP achieve lasting remission with corticosteroids [65-68] and long-term treatment is associated with multiple well-documented, dose-related adverse effects, as well as an increased risk of infection [69, 70] (**Table 1**). Over time, these detrimental effects may outweigh their benefits. IVIg and Anti-D also produce only short-lasting responses and are associated with significant toxicities, as well as risks inherent to pooled blood products such as transmission of infections (**Table 1)**.

Immunosuppressive agents (azathioprine, cyclosporine, cyclophosphamide) are not curative and often not well tolerated (**Table 1**). Suppressing the immune system may predispose patients to infection. Indeed, infections account for approximately half of all deaths in patients with ITP [6, 11]. Alkylating agents should be avoided in those who plan to have children and immunosuppressants should not be given to pregnant women. Cyclosporin A should be used very carefully in the elderly and avoided in those with renal insufficiency.

While the TPO mimetics look to be a promising treatment option, long-term data are limited, especially for eltrombopag, although 5-year safety and efficacy data have recently been reported for romiplostim [44]. In general, continued treatment is required to maintain the treatment response and rebound thrombocytopenia has been seen after stopping treatment. The clinical significance of increased bone marrow reticulin in patients treated with TPO mimetics [34, 43, 46] is yet to be clarified. Hepatotoxicity has been seen with eltrombopag [50] and monitoring of liver function is recommended during treatment [49]. Possible risks of TPO mimetics include thrombotic/thromboembolic complications if platelet counts exceed the normal range, although ITP itself may be associated with increased thromboembolic risk [71]. As these agents stimulate the TPO receptor there is also the theoretical possibility that they might stimulate progression of existing haematopoietic malignancies or Myelodysplastic Syndromes (MDS) [42, 49].

In Europe, romiplostim is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Nplate may be considered as second-line treatment for adult non-splenectomised patients where surgery is contra-indicated [42, 49]. However, this is not the case in the USA, where both romiplostim and eltrombopag are available for use in patients with chronic ITP, regardless of splenectomy status [72, 73].

Data supporting the use of rituximab in chronic ITP are limited, being derived mainly from case series. Randomised controlled trials are required to establish the efficacy of the drug. Available data show long-term efficacy and safety concerns, with only a minority of patients maintaining a long-term response. Patel et al. found that almost half of patients with a response duration >1 year relapsed over a 5-year follow-up [74]. While reported toxicities (**Table 1**) have occurred mainly in patients being treated for lymphoma and the risk may be lower in ITP patients, the risk: benefit is likely to differ considerably between these two settings.

5. Quality of life and cost issues.

For patients who achieve an adequate platelet response to splenectomy, the disease burden is minimised, with less bleeding symptoms, fatigue, and concerns over everyday life. They may be free from ITP medication for years if the platelet response is maintained.

Clearly, financial considerations may impact the choice of treatment modality. Successful splenectomy is a once-only cost, provided that accessory spleen exploration is not required, and may be similar to that of a single course of IVIg [75]. In contrast, immunosuppressive treatments usually need to be continued long-term, although dose reduction may be possible and some patients can even maintain long-term remissions off-therapy. With the TPO mimetics continued treatment is generally required to sustain the response [34].

Reimbursement will differ between countries and not all would reimburse for costly new medical treatments in a patient who refuses splenectomy. Additionally, in some developing countries, the range of available treatments may be restricted.

Conclusions

Generally accepted criteria for splenectomy in patients with chronic ITP include severe thrombocytopenia (platelet count $<10 \times 10^9$/L) or platelet counts $<30 \times 10^9$/L with high risk of bleeding; and the requirement for continuous corticosteroid therapy to maintain 'safe' platelet counts [76]. In 1996, George et al. [2] noted that there were 'inadequate data to make evidence-based recommendations on the appropriate indications and timing for splenectomy, on when the benefits of splenectomy might outweigh its potential harms, and on appropriate preoperative management.'

Since that time, increasing clinical knowledge has allowed development of effective targeted therapies including the TPO mimetics. With these agents, it may be possible to 'buy time' for patients who are unable or unwilling to undergo splenectomy, maintaining a safe platelet count while allowing for a chance of spontaneous remission, and thereby deferring splenectomy for prolonged periods. Thus, some physicians argue that in general, this irreversible and immunocompromising procedure should not be performed before exhausting available medical treatment options. There are some exceptions, such as patients who wish to become pregnant, those who are 'sick of' or cannot receive medical treatments. With the emergence of new treatment options, it is likely that many well-informed patients will refuse splenectomy.

On the other hand, splenectomy does offer a very good chance of cure, with the possibility of being free from ITP medication for many years if the platelet response is maintained. With advances in surgical practice and management, the risks are well identified and acceptable. Progress has been made towards predicting which patients will respond, although testing is not widely available and predictors of response have not been fully validated. Moreover, new medical treatment options such as the TPO mimetics are now available for patients in whom splenectomy fails, as well as those in whom splenectomy is contraindicated.

Thus, the decision whether to proceed to splenectomy or try other medical therapies in corticosteroid-refractory patients remains patient-specific. There are no data to demonstrate better outcomes if this procedure is performed early on in the disease course and it is hoped that the treatment algorithm will become clearer in the near future as more information on newer treatments becomes available. Ultimately, identifying the 'right patient at the right time' requires careful weighing of the risks of splenectomy with the expected benefits for the individual, as well as full discussion with the patient.

Acknowledgements

This article is based on a debate between the authors, which took place in Berlin, Germany on June 4th 2009 during the 14th European Haematology Association Congress and was supported by Amgen Europe GmbH, Zug, Switzerland. The authors thank Julia Balfour, Medical Writer, Kilconquhar, Scotland for assistance with the preparation of the manuscript, with financial support from Amgen.

Conflicts of interest disclosures

Authors conflict of interest declarations are as follows: Prof. Newland - Research funding from Amgen, Baxter, GSK and Genentech; consultant and speaker for Amgen and GSK; advisory board for GSK and Pangenetics; Dr. Stasi - advisory boards and/or speaker for GSK and Amgen. Dr Pabinger – speaker and advisory boards for Amgen and GSK. Dr Thornton has no conflicts of interest to declare.

Figure 1. Treatment options for chronic ITP.

* indicates treatments with minimal data and considered to have potential for considerable toxicity [3].**§ The IV anti-D product Winrho SDF was withdrawn from the European market in 2009.**

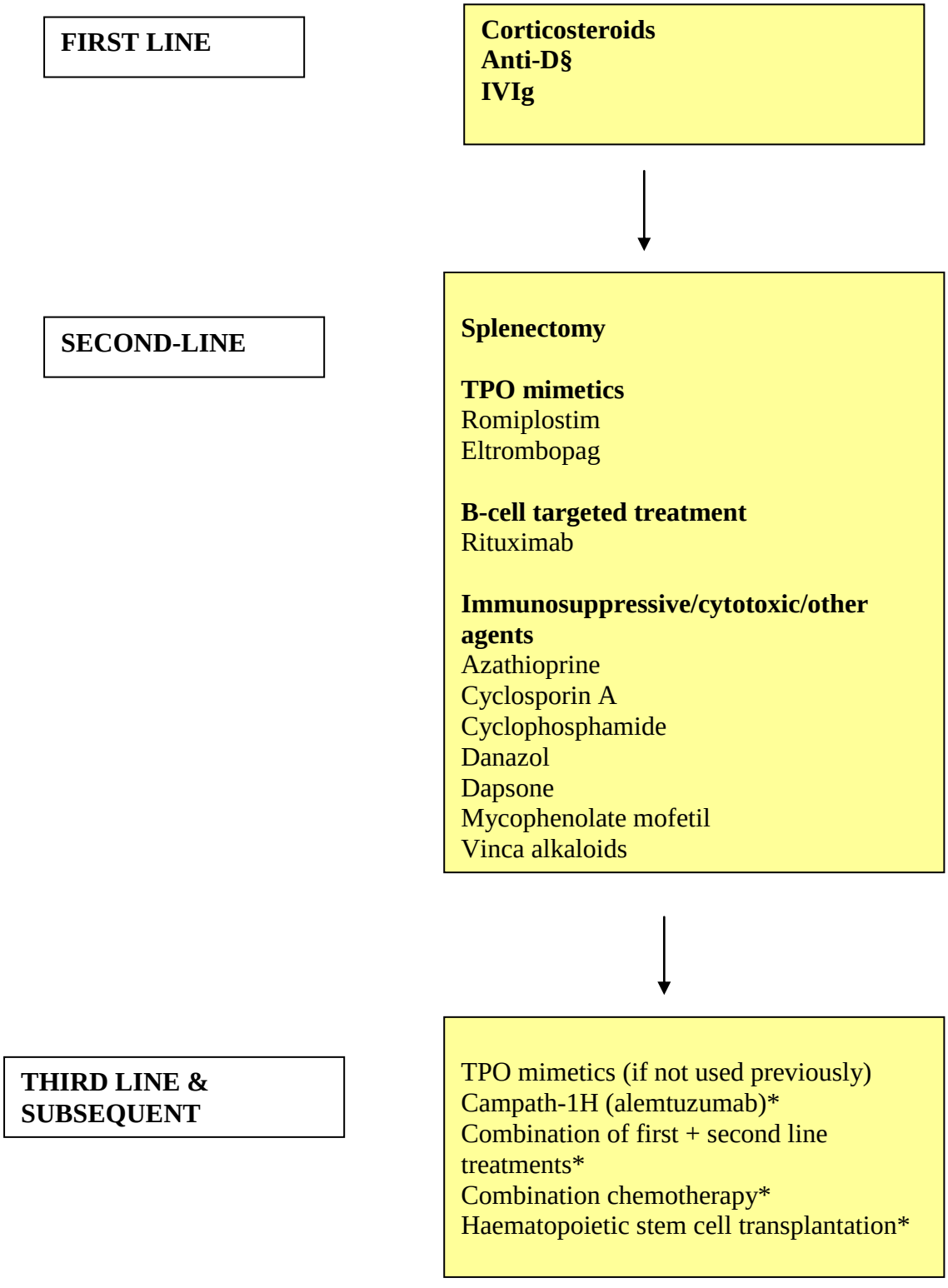


Figure 2. Response and relapse rates in patients undergoing splenectomy. Response rates shown are based on pooled data from 47 case series in a total of >2000 adults (n=2623 for complete response and 2116 for overall response analysis). Relapse rate (median shown) is based on 85 case series in 3355 adults and children (median follow-up 33 months) [10].

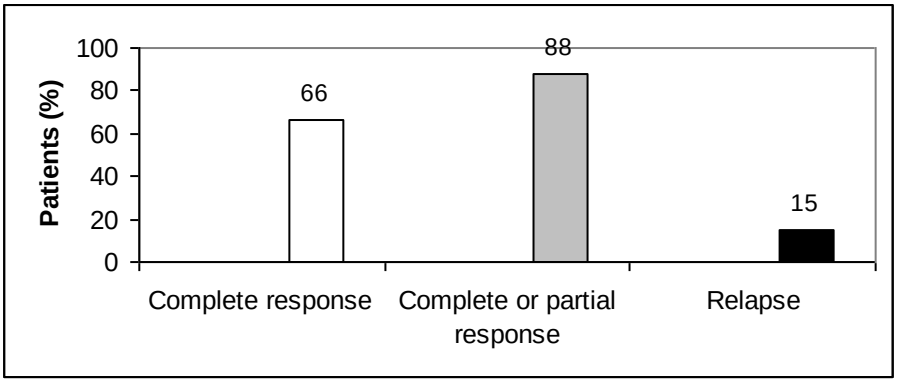


Figure 3 . Death and non-response rates over a 12-year follow-up of patients with chronic ITP who failed splenectomy and required further treatment (n=105 for response analysis and n=108 for mortality analysis) [24]. (Note that the 'unresponsive' and 'death' categories are not mutually exclusive).

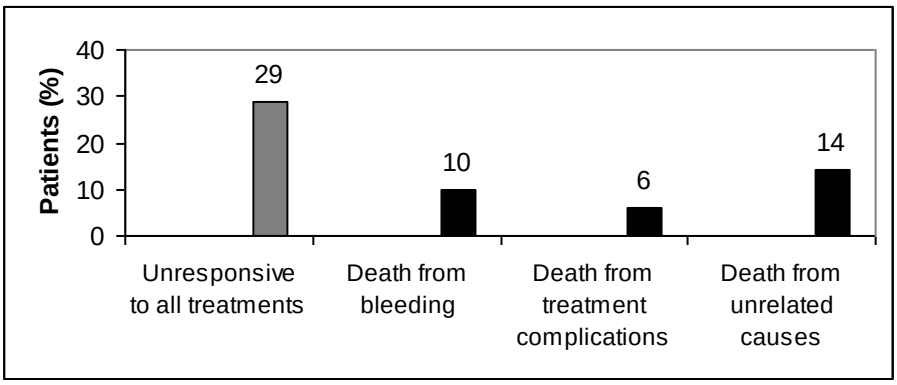
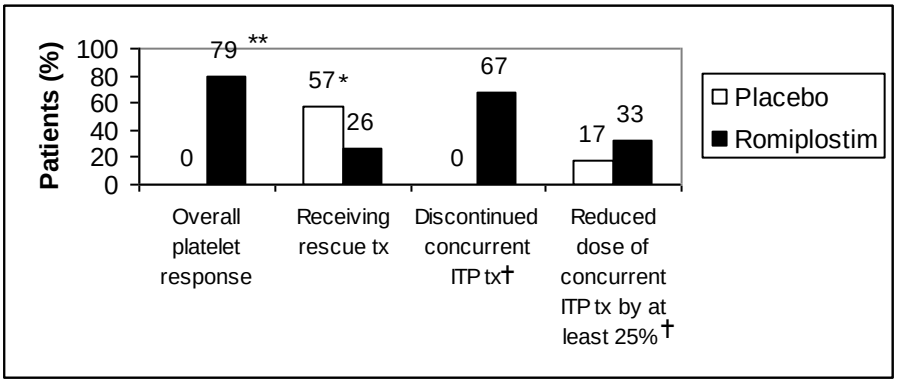


Figure 4. Results of two parallel phase III trials of romiplostim (starting dose 1 mcg/kg, adjusted to achieve and maintain a target platelet count of 50-200 x 10^9/L) in (a) splenectomised and (b) nonsplenectomised patients with severe and chronic ITP (baseline platelet count 2-31 [median 16] x 10^9/L) [34]. Overall platelet response was defined as a durable platelet response (platelet count ≥50 x 10^9/L for ≥6 weeks of the last 8 weeks of treatment with no rescue medication used during the study) or ≥4 weekly platelet responses (≥50 x 10^9/L) at any time during the study. * P < 0.05; ** P < 0.01; † = expressed as a percentage of those taking concurrent ITP medication; tx = treatment.

(a) Splenectomised patients



(b) Nonsplenectomised patients

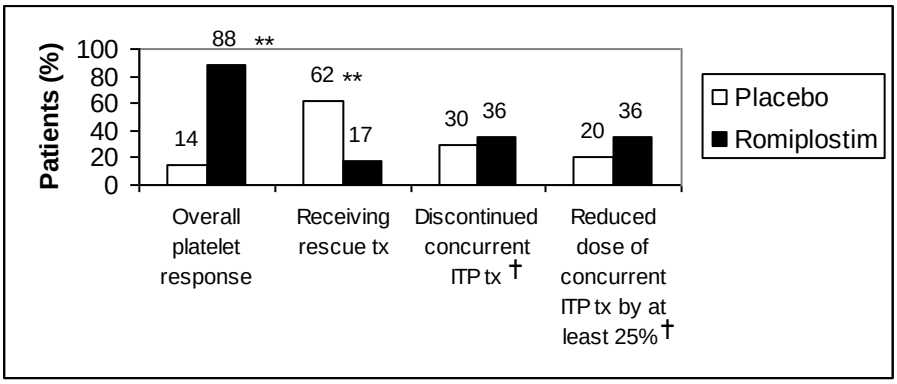


Table 1. Summary of response rates and adverse effects associated with first and second-line treatments used for ITP. *The IV anti-D product Winrho SDF was withdrawn from the market in 2009 because of safety concerns.

Treatment	Initial response rates/time to response/duration of response [3]	Risks/adverse events
First-line		
Corticosteroids	70-80%/several days –several weeks/?[a]	Weight gain, cushingoidism, mood swings, insomnia,hypertension, osteoporosis, immunosuppression, increased risk of infection, peptic ulcer, hyperglycaemia, psychosis, glaucoma, cataract, impaired wound healing, skin changes, adrenal insufficiency [69]
IVIg	≤80%/2-4 days/2-4 weeks	Headache, fever, nausea/vomiting, allergic reactions/anaphylactic shock, hypotension; reversible haemolytic anaemia [77] Risks associated with pooled blood product e.g. transmission of infections
IVAnti-D	≤80%/4-5 days/3-4 weeks	Malaise, fever, chills, nausea/vomiting, anaphylaxis, cutaneous reactions, hypotension, tachycardia, life-threatening intravascular haemolysis [78, 79]* Risks associated with pooled blood product e.g. transmission of infections Restricted to Rhesus-positive, nonsplenectomised patients
Second-line		
Splenectomy	80%/1-24 days/5-10 years in 67% of patients	General risks of surgery (complications of general anaesthesia, bleeding, wound infection, thrombosis); perioperative complications: pneumonia, transient/prolonged ileus, need for transfusion, overwhelming post-splenectomy infection [10-13, 15, 80, 81] Long-term vascular complications: thromboembolism/atherosclerosis, pulmonary arterial hypertension [16, 24, 71, 82-84]

TPO mimetics		
Romiplostim	Nonsplenectomised 88%; splenectomised 79%/1-4 weeks/sustained with continued administration	Romiplostim: arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, paraesthesia [72]. Eltrombopag: nausea, vomiting, menorrhagia, myalgia, paraesthesia. cataract, dyspepsia, hepatotoxicity [73]. Both: rebound thrombocytopenia after stopping treatment, increased bone marrow reticulin, immunogenicity, Hypothetical risks: thrombotic/thromboembolic complications, progression of existing haematopoietic malignancies or Myelodysplastic Syndromes (MDS), alterations in blood cell parameters [34, 38, 39, 42, 43, 47, 50, 85, 86].
Eltrombopag	59%/ 2 weeks/sustained with continued administration[43]	
B-cell targeted treatment		
Rituximab	60%/1-8 weeks/variable	Infusion reactions on first infusion (fever, chills, rash, sore throat, bronchospasm, anaphylaxis, serum sickness) Risk of fatal adverse events (infusion reactions; severe mucocutaneous reactions; PML; hepatitis B reactivation) Contraindicated in those with active hepatitis B infection [53, 57, 58]
Immunosuppressive/cytotoxic/other agents		
Azathioprine	40-67%?/slow/≤25% have sustained response off therapy	Weakness, sweating, increased transaminases, severe neutropenia with infection[87-89]
Cyclophosphamide	24–85%/1-16 weeks/≤50% have sustained response	Neutropenia, acute deep venous thrombosis, nausea, vomiting, risk of secondary malignancies [90-94]
Cyclosporin A	50-80% in small studies/3–4 weeks/>50% of responders have sustained response at 2 years with low-dose treatment	Fatigue, renal insufficiency; hypertension, neuropathy, gingival hyperplasia, myalgia, dyspepsia, hypertrichosis, tremor Unsuitable for elderly and those with renal insufficiency [95, 96]

Danazol	≤67%/3–6 months/?	Acne, hirsutism, elevated cholesterol, amenorrhea, increased transaminases [97]
Dapsone	≤50%/3 weeks/sustained response in ≥67% off treatment	Infrequent and treatable/reversible abdominal distension, anorexia, nausea, methaemoglobinuria; skin rash (may require discontinuation)[98] Risk of haemolytic anaemia in patients with G6PD deficiency [99]
Mycophenolate Mofetil	≤75%/4-6 weeks/short duration	Headache, backache, abdominal distension, anorexia, nausea. Long-term toxicities unknown [100]
Vinca alkaloids	Variable10-75%/5-7 days/?	Neuropathy, neutropenia, fever, infusion site reactions [101]

a. Data shown for prednisolone 0.5-2mg/kg for 2-4 weeks.
PML = Progressive Multifocal Leukoencephalopathy

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***Conflict of interest**

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