Current Management of Primary Immune Thrombocytopenia

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ABSTRACT

Primary immune thrombocytopenia is an autoimmune disorder of unknown cause affecting both children and adults. The low peripheral blood platelet count is caused by premature platelet destruction by self-reacting antibodies in addition to an impairment of platelet production. The disease is heterogeneous in its pathophysiology, clinical features and responses to treatment. To date, most of the treatments used have been immune-modulating drugs and these contribute to increased morbidity and mortality in patients. A new class of drugs, the thrombopoietin receptor agonists, has been developed for use in ITP. These have gone through randomised controlled trials in large numbers of patients with ITP. These drugs have high efficacy and are well tolerated. In addition, around 30% of patients receiving these drugs are able to stop them and maintain a safe or normal platelet count. Older treatments such as splenectomy are being used less than before, largely because of the introduction of the thrombopoietin receptor agonists. Currently there are trials underway evaluating novel therapies for ITP that will become available over the next few years once the trials are complete.

Keywords: Eltrombogag; Immune thrombocytopenia; ITP; Management; Romiplostim; Second-line therapy; Sustained responses; TPO receptor agonists

INTRODUCTION

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disorder affecting both children and adults, characterised by a platelet count below $100 \times 10^9/l$ [1, 2]. Clinical manifestations include petechiae, purpura, bruising, and overt bleeding. Previously, ‘acute ITP’ was used to describe a self-limited form of disease and ‘chronic ITP’ thrombocytopenia described the disease if is lasted for more than 6 months. In 2009 new terminology for ITP was agreed upon based on the duration of the disease. The new terms for ITP are: ‘newly
diagnosed’ (from diagnosis until 3 months), ‘persistent ITP’ (3–12 months) and ‘chronic ITP’ (ITP lasting for more than 12 months) [2]. Chronic primary ITP in adults is slightly more common in women of childbearing age but the sex incidence is similar in patients over 60 [2, 3]. The incidence of ITP in adults is around 4 per 100,000 people per year, with a UK prevalence of up to 24 per 100,000 people [4–6].

Bleeding is highly variable and there is great heterogeneity in primary ITP. Bleeding is most commonly mucocutaneous, involving gum bleeding, blood blisters in the mouth and menorrhagia. Major bleeding is not common if the platelet count is above $30 \times 10^9/l$. The most serious form of bleeding, intracranial haemorrhage, is rare and is most often seen in older patients who have additional comorbidities and in patients who fail to respond to therapy [7]. The yearly risk of fatal haemorrhage is around 1.6–3.9% [8]. This risk varies with age, at 0.4% per annum in those below the age of 40 years to 13% per annum over patients over 60 years of age.

The aims of this review are to provide a brief overview of ITP and its current management. The main emphasis of the review is on the recently introduced TPO receptor agonists focussing on published trial data. Both romiplostim and eltrombopag are discussed in detail, including recently published studies that show the unexpectedly high rate of sustained responses to these agents following their discontinuation.

**CLINICAL FEATURES**

Paediatric and adult ITPs are quite different in terms of their underlying pathophysiology and clinical outcomes. In children, ITP may follow a viral infection or immunisation. In most children the disease remits spontaneously by 6 months with little need for medical treatment. Around 15% of children will go on to develop chronic ITP.

In the adult form of the disease there is usually no prodrome. Instead, the patient may notice an increase in bruising, or petechiae. In many cases ITP in adults is picked up by chance when the patient has a full blood count for other reasons, for example, preoperatively. This is seen particularly in the elderly when nearly a third will be diagnosed by chance.

ITP in adults is extremely heterogeneous. Many patients have no clinical problems related to their thrombocytopenia even at very low platelet counts, while other patients may have bleeding from the outset and a study of practice in Europe over 1 year showed that 40% of patients had no bleeding at all despite low platelet counts and required no treatment [9]. The platelet count by itself is an unreliable predictor of clinical outcome. Many factors contribute towards the bleeding risk including age, comorbidities, medication, prior bleeding history and other factors not yet identified. In some patients an autoantibody may bind to a critical epitope on the platelet glycoprotein and interfere with platelet function. Autoantibodies reacting with glycoprotein (GP)IIb/IIIa may affect platelet aggregation; these are the most common autoantibodies seen in primary ITP [10]. Antibodies against GPIb/IX may impair platelet adhesion to the subendothelial matrix, thereby causing severe bleeding for the level of platelet count. Other autoantibodies including antiphospholipid antibodies are detected in up to 30% of patients with ITP. These may affect platelet and vascular function. Overall, however, despite the severity of the thrombocytopenia, severe bleeding is not common in ITP, in contrast with
thrombocytopenia following chemotherapy or bone marrow failure [11].

**MANAGEMENT OF ADULT ITP**

ITP in adults is a disease with low morbidity and mortality. Most patients with ITP have few problems related to the thrombocytopenia but a minority may be resistant to treatment and have a platelet count that is chronically low. After the publication of the original American Society of Hematology guideline in 1996 [12] there was a tendency to treat most patients whose platelet count was <30 × 10^9/l. Most of the treatments available until fairly recently had significant side effects for many patients. Because of the immune suppression often used to treat ITP, patients are at increased risk of infection. A study of 152 consecutive adult ITP patients published by Portielje and colleagues showed that the treatments used contributed significantly to an increase in morbidity and mortality in their cohort [13]. Contrary to what might be expected, half of the deaths observed in the study were attributable to the treatment used rather than haemorrhage. MacMillan showed this to be a particular problem in patients who had failed splenectomy and required continuing immune suppressive therapy [7].

Patients with ITP who have low platelet counts bleed less than patients with aplastic anaemia or chemotherapy-induced thrombocytopenia at equivalent platelet counts. For this reason, in addition to the toxicities of the treatments used discussed earlier, there has been a relaxation in the platelet thresholds for treatment. The International Consensus Report [3] suggested not treating patients whose platelet counts were >50 × 10^9/l. At this platelet count most patients will have few symptoms or signs of ITP. Patients whose platelet counts are lower may also require little treatment depending on their age, comorbidities and bleeding history. Overall the number of patients with ITP who are on no treatment has risen over the past decade whilst the number of patients receiving medical treatment has fallen.

The main aim of treatment is to achieve a safe platelet count for each patient on a case-by-case basis [14]. The intention is not to normalise the platelet count. In general, treatment is seldom required when platelets are greater than 20 × 10^9/l. For patients with platelets less than 20 × 10^9/l treatment may be required but this depends on a full assessment of the patient including lifestyle, occupation, bleeding history, comorbidities and other factors.

Initial first-line treatment has remained unchanged for decades and comprises corticosteroids [15], IVIg [16, 17] and anti-D [18] in countries where the latter is available. Corticosteroids are cheap, raising platelet counts rapidly within 1–2 days in around 75% of patients. However, long-term responses are seen in only 25% of patients. Side effects are extremely common and predictable. Currently available corticosteroids include prednisone, prednisolone, methylprednisolone and dexamethasone. Prednisolone has been used predominantly as first-line treatment rather than dexamethasone but recent studies of the latter suggest that the response rates are higher and prolonged remission is seen more commonly [19]. However, despite this, prednisolone remains the first-line corticosteroid of choice [3].

There have been several trials of IVIg in ITP since its first use in the mid-1980s. The response rate in ITP is similar to that of corticosteroids but the time to response is shorter, with a response normally seen within 24 h although
most are transient rarely exceeding 3–4 weeks. Toxicities include headache, renal impairment and thrombosis.

Intravenous anti-D is effective in 80% patients with primary ITP and is suitable for those who are Rh(D) positive and have not undergone splenectomy. The infusion time is shorter than for IVIg and the donor pool from which it is derived is much smaller than that of IVIg. Anti-D has been shown to induce a longer response time than IVIg [20] and may also reduce the need for splenectomy [21].

SECOND-LINE THERAPY

If a patient fails to respond to first-line treatment or relapses following a response there may be a need to introduce a second-line treatment. These treatments include medical therapies and splenectomy. The medical treatments used as second-line therapy have undergone few randomised controlled trials and a systematic review covering nearly 700 patients showed that complete remission rates rarely exceed 15% and few of the individual studies have sufficiently large numbers of truly refractory patients to make a definitive recommendation [22]. Most of these drugs are not licensed for ITP and have been chosen because of their efficacy in other autoimmune diseases or in post-solid organ transplant immune suppression. The recent International Consensus Report provides a list of second-line therapies placed in alphabetical order because there were insufficient data to rank the treatments in order of efficacy, apart from the thrombopoietin receptor agonists, which have undergone rigorous randomised trials [3].

The immunosuppressants azathioprine, ciclosporine and mycophenolate have shown most efficacy in adult ITP although most studies are small. These are in general small, open studies and response rates should be considered with some scepticism. Azathioprine produces complete responses in 45% of patients [23]. Ciclosporine has been shown to improve platelet counts in one study of 80%, with 42% patients achieving a complete response [24, 25]. Durable remissions have been reported after ciclosporine has been stopped [25]. Side effects include fatigue, renal insufficiency, hypertension and neuropathy. Mycophenolate mofetil has been shown to be of value in ITP. This immunosuppressant is similar to azathioprine and ciclosporine and is an anti-proliferative agent [26]. An overall response rate of 78% has been reported. Interestingly, prolonged remissions of 25% have been reported in patients on mycophenolate [27].

Rituximab is been licensed for rheumatoid disease and has been used for some years in ITP with initial responses of 60% and durable responses of 15–20%. However, there are safety issues with rituximab including progressive multifocal leucoencephalopathy (PML) and hypogammaglobulinaemia in addition to the lack of approval for its use in ITP [28–30]. A more recent randomised placebo controlled study using rituximab in the second-line setting demonstrated a much less favourable response, and although those who achieved CR on rituximab had a more durable response the benefits were small [31]. For these reasons rituximab usage will probably decline particularly with the wide availability of the newer TPO receptor agonists. Rituximab may be used at the standard dose (375 mg/m²) or low dose at 100 mg weekly for 4 weeks [32]. Response to rituximab is generally seen after 1–2 weeks but in some patients a response may be seen up to 2 months after the last infusion [28, 30].
Cyclophosphamide, an alkylating agent, has been used successfully in adult ITP. It can be given orally at 1–2 mg/kg/day for up to 4 months or it may be given IV at 0.3–1 g/m² for between 1 and 3 doses every 2–4 weeks. The reported response rate is 24–85% [33, 34].

Danazol is an attenuated androgen and is given orally at 200 mg between two and four times per day. The response rate is around 60% [35]. Danazol may be more effective in older females and those patients who have not undergone splenectomy [35].

Dapsone is an anti-leprotic drug that has been used successfully in ITP. It is usually given at 75–100 mg/day orally. Responses may be seen in up to 50% patients [36]. Because of its risk in glucose-6-phosphate dehydrogenase deficiency, at-risk males should be screened for this before starting dapsone. It is however a very cheap form of treatment and is widely used in the developing world.

Splenectomy has been used as a second-line treatment for ITP for 100 years [37]. Following splenectomy there is an early response rate of 80% but over time relapses occur and the long-term response rate is closer to 66% [38–40]. Even if splenectomy fails to induce a complete remission, many patients may still experience a partial response to splenectomy with a platelet count that is higher than that before splenectomy [12, 41].

Since splenectomy is a surgical procedure there are risks associated with this including bleeding, thrombosis and infection. Complication rates are highly variable depending on a number of factors [13, 38, 39, 42, 43] and are higher in older patients [44] and in open splenectomy compared to laparoscopic splenectomy [39].

A number of tests for predicting the likely response to splenectomy have been proposed including response to corticosteroids or IVIg [45] but these are seldom used as predictors. The best current method for predicting response to splenectomy is the indium-labelled platelet survival scan [46–48]. For patients in whom the platelet destruction is pure or predominantly splenic the chance of a response to splenectomy is around 90% [49]. Unfortunately this test is only available in a few centres worldwide.

Before carrying out splenectomy patients should be vaccinated against Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis [3]. These vaccines may not be effective in patients who have received rituximab in the 6 months prior to splenectomy. Following splenectomy patients should be given prophylactic antibiotics such as phenoxymethylpenicillin 250–500 mg twice daily or the equivalent if allergic, possibly for life, although there is no consensus on the exact duration of the prophylaxis. In addition, patients should keep a supply of broad-spectrum antibiotics at home, which they should take if infection is suspected. They are also advised to seek immediate medical attention [50].

With the availability of the TPO-receptor agonists and the long-term responses these may induce one might argue against splenectomy being a valid second-line therapy today. The rate of splenectomy for ITP is falling worldwide and many patients would benefit from deferring splenectomy until they have tried other lines of treatment including TPO-receptor agonist. Unpublished data from the UK Adult ITP Registry have shown a 10% reduction in splenectomy rates since the publication of the International Consensus document [3]. Even if their platelet count is low it may be safe enough for normal day-to-day living with no requirement for splenectomy.
THROMBOPOIETIN RECEPTOR AGONISTS

TPO is the primary factor regulating platelet production [51]. Several TRAs have been developed that activate the TPO receptor and increase platelet production [52–56].

Two drugs, eltrombopag and romiplostim, are currently FDA-approved for use in adult ITP. These second-line agents represent a new class of treatment for ITP. TRAs stimulate megakaryopoiesis, inducing megakaryocyte proliferation and differentiation with an increase in platelet count. From phase I–III trials both drugs are highly effective at raising platelet counts in healthy volunteers and patients with chronic ITP [57, 58]. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

ROMIPLOSTIM

This molecule is an Fc peptide fusion peptibody. The module consists of a 14-amino-acid peptide dimer covalently linked to two disulphide-bonded human IgG1 kappa light chains. This carrier Fc protein prolongs the half-life of the drug. Romiplostim stimulates megakaryopoiesis after subcutaneous injection. The rise in platelet count is dose-dependent and patients start treatment of 1 μg/kg bodyweight weekly increasing by 1 μg/kg weekly until the desired platelet count is achieved [58].

The initial phase I double-blind placebo-controlled trial involved 48 healthy volunteers [59]. Those receiving romiplostim by single IV injection at 10 μg/kg showed elevated platelet counts at over 1000 × 10⁹/l. The first study in patients with ITP used a dose of 0.2–10 μg/kg on days 1 and day 15 [52]. Seven of 12 patients at 3, 6 or 10 μg/kg achieved a platelet count of greater than 50 × 10⁹/l. The open dose escalation phase I/II study investigated the safety and efficacy in 16 patients with platelets less than 30 × 10⁹/l [60]. Doses between 30 and 500 μg were given on days 1 and 15. Platelet counts of 50 × 10⁹/l or greater were seen in all patients. Two parallel phase III studies were carried out in Europe and the USA [55]. Twenty-four of 52 patients were treated with 1 μg/kg or placebo every 7 days with dose adjustment based on platelet counts. One hundred twenty-eight patients were recruited and all of these has severe and refractory ITP. One-third were taking concomitant medication. Sixteen of 42 on romiplostim had a durable response (platelets greater than 50 × 10⁹/l for at least 6 out of the last 8 weeks treatment) in the splenectomised group and in 25 of 41 in the non-splenectomised arm. Combining both durable and transient responses 36 out of 41 were seen in the non-splenectomised group and 33 out of 42 in the splenectomised group. There was no recorded risk of thromboembolism in the romiplostim arm [61].

The 12-week study of romiplostim versus placebo was carried out in splenectomised and non-splenectomised Japanese patients with chronic severe ITP [62]. The mean increase in platelet count from baseline was 110 × 10⁹/l in those receiving romiplostim compared with 2 × 10⁹/l in the placebo arm.

Results are available for up to 5 years continuous dosing involving 292 adults. Platelet counts of greater than 50 × 10⁹/l were recorded at least once by more than 95% of subjects in the study [63]. Ninety-eight per cent experienced adverse events during the follow-up period including headache in 38%, fatigue in 32%, contusion in 31%, upper respiratory tract infection in 26%, diarrhoea in
25% and epistaxis in 25%. Nineteen patients experienced 25 thromboembolic events (arterial and venous equally). There was no association with platelet count and only six of these were considered to be related to romiplostim.

Neutralising antibodies to romiplostim were found in two patients (1%). These antibodies were measured when the patients’ platelet counts fell. Antibodies became undetectable after romiplostim was stopped and no cross-reactivity with endogenous TPO was seen.

**ELTROMBOPAG**

This is a small molecule of 564.6 Da molecular weight. Eltrombopag is one of the naphthalenesulfonic acids with a potency similar to native TPO [64]. Eltrombopag stimulates megakaryopoiesis in vitro [65]. A phase I study, similar to that of romiplostim, showed a dose-dependent rise in platelet counts [57] and a randomised double-blind placebo-controlled phase II study confirmed both its efficacy and safety [53]. The first phase III study was a 6-week double-blind randomised controlled trial in chronic severe ITP with platelets less than $30 \times 10^9/l$. Eltrombopag showed a response rate of 59% compared to 16% with placebo. Common adverse events where non-serious and transient. Deranged liver function tests were seen in some patients.

A 6-month study, RAISE, a randomised controlled double-blind study to evaluate efficacy, safety and tolerability, was conducted [66]. Platelets of over $50 \times 10^9/l$ were seen in 106 (79%) patients in the eltrombopag arm compared to 17 (28%) in the placebo arm. Concomitant medication was reduced by 59% in the eltrombopag arm compared to 32% in the placebo arm. Rescue medications were reduced with only 18% in the eltrombopag arm requiring rescue medication compared to 40% requiring rescue medication in the placebo arm. The risk of bleeding was 76% lower in the eltrombopag arm. Thromboembolic events were reported in 2% of patients (0 in the placebo arm). There was a 7% increase in transaminases in the eltrombopag arm compared to only 3% in the placebo arm.

EXTEND was an open-label study that recruited patients who had been enrolled in previous eltrombopag studies [67]. A total of 299 patients were treated with eltrombopag for up to 3 years. No new safety issues were reported. Most patients achieved a platelet count response at least once during this period (80% of splenectomised and 88% of non-splenectomised). Responses were maintained for a median of 73/104 cumulative weeks for the non-splenectomised arm.

**TRAs MAY INDUCE SUSTAINED REMISSIONS**

Romiplostim and eltrombopag are licensed for use in adults with chronic ITP. The drugs stimulate megakaryocyte proliferation and platelet production. The expectation when using these agents is that the platelet count will rise when taking the TRA but will drop to baseline levels when the drug is stopped. These drugs were not licensed with any curative intent. However, published reports show that a proportion of patients may achieve a sustained response to the TRAs even after the drugs have been stopped.

One study of 54 adults treated with at least one TRA over a 5-year period found that 20 of 28 patients (28.5%) who achieved a complete response had a sustained response after stopping the TRA. The median follow-up was 13.5 months. No factors predictive of sustained response were identified [68]. In another study, 46 patients with primary ITP were treated using
a TRA. Eleven of 46 patients (24%) were able to stop the TRA (7 romiplostim, 4 eltrombopag) and sustained their platelet counts. Again no predictive factors of sustained response were found [69]. Ghadaki and colleagues reported sustained responses in 9 of 31 patients (29%) treated with a TRA. Four of the nine patients subsequently relapsed [70]. Provan et al. reported sustained responses after discontinuing romiplostim in 5 of 21 patients (24%). All patients had received multiple prior therapies. The median duration of the romiplostim administration was 26 months (range 7–60 months). As with previous studies no predictive factors were identified [71]. A more recent phase 2, single-arm study looked at 75 patients less than 6 months from presentation who had failed first-line treatment and had a continuing platelet count of less than 30 treated with romiplostim [72]. Responses occurred rapidly in more than 90% and long-term remission occurred in 32%, which were sustained for more than 6 months off all treatment. Again no predictive clinical features could be identified but the studies confirm that a significant proportion of patients can safely stop treatment.

A large series of patients (260) treated with eltrombopag was evaluated by Gonzalez-Lopez and colleagues [73]. Out of 49 evaluable patients, 26 (53%) had a sustained response after stopping eltrombopag with a median follow-up of 9 months.

From the published data, therefore, it would appear that 25–30% of patients receiving a TRA may expect a sustained response on stopping the drug. The mechanism for these sustained responses is not clear. Some of these patients may have had a spontaneous remission but the patients in all reported studies had received several prior treatments and had severe thrombocytopenia for some considerable time. Spontaneous remission is therefore unlikely. The TRAs may have an effect on regulatory T cells (Tregs). These cells naturally suppress autoimmune disease [74]. From studies of rituximab used for the treatment of ITP it would appear that those patients who respond to rituximab normalise their Tregs; those that fail to respond to rituximab do not [75]. The use of the TRAs may have an effect on the Treg compartment returning Tregs to normal number and function, thereby restoring tolerance. However, this has not been confirmed to date.

Alternatively, tolerance may be induced by increasing megakaryocyte and platelet mass through the use of TRAs in much the same way as giving large doses of factor VIII is used to induce tolerance in acquired haemophilia.

Clearly more basic science is required in order to determine the underlying mechanism leading to sustained responses in these chronic ITP patients.

**CONCLUSION**

Over the past decade, and certainly since the publication of the International Consensus Report [3] and revised American Society of Hematology guidelines [76], there has been a major change in the way ITP is managed. Patients are now treated based on symptoms and signs rather than using an arbitrary platelet threshold. Because of this fewer patients are receiving medical therapies for ITP. Previously used treatments for ITP had low efficacy and considerable side effects for many patients. With the introduction of the TRAs the management of ITP has been transformed. These new agents have very high efficacy and few side effects. The TRAs are effective in even the most refractory patients who can expect to achieve a platelet count that is safe and in many
cases a normal platelet count. It should be noted, however, that the TRAs should not be used to normalise the platelet count but rather achieve a safe platelet count. After being on a TRA for some time, perhaps a year or 2, around 25–30% of patients may achieve a sustained remission with safe or normal platelet counts off therapy. The underlying mechanisms inducing these sustained responses remain to be elucidated.

There are also on-going trials of other treatments with new classes of drugs such as Syk inhibitors (fostamatinib), antibody therapies such as anti-CD40 ligand (anti-CD154), GMA161 (anti-CD16), dacluzumab and alemtuzumab, avatrombopag [77], and others. Once these have been approved for use patients with ITP should expect to have a much higher quality of life because of the low incidence of toxicities and high efficacy of these newer agents with fewer patients receiving the older types of immunosuppressive therapy.

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