New therapeutic options for immune thrombocytopenia

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ABSTRACT

Understanding of the mechanisms and aetiology of immune thrombocytopenia (ITP) has progressed significantly in recent years. It is now recognised to be an autoimmune condition, involving not only platelet destruction, but also deficits in platelet production. This has led to widespread research exploring potential mechanisms for therapy, the result of which has been the development of romiplostim and eltrombopag. These new treatments target the thrombopoietin receptor (TPO-R), promoting formation of megakaryocytes and survival of platelets.

Furthermore, the advances in the understanding of ITP have led to the production of guidelines to assist healthcare professionals in the diagnosis and treatment of ITP. This review examines the recommendations made in these guidelines, particularly the American Society of Haematology (ASH) 2011 evidence-based practice guidelines. In addition, searches were carried out to retrieve information on clinical trials of new molecules and off-label treatments for ITP.

Corticosteroids, anti-Rho(D) immunoglobulins (anti-D), intravenous immunoglobulins (IVIg) and splenectomy are well-established treatments and continue to be recommended in the guidelines. The recently available romiplostim and eltrombopag, which are specific for treatment of ITP, are also included in the recommendations. The only off-label therapy to be recommended in the guidelines is the chimeric monoclonal antibody rituximab. However, investigations are ongoing into products approved for other indications, which may be beneficial to patients suffering from refractory ITP.

KEYWORDS

Immune thrombocytopenic purpura, treatment, corticosteroids, intravenous immunoglobulin, splenectomy, rituximab, romiplostim, eltrombopag

INTRODUCTION

Since 1965 it has been recognised that platelet destruction caused by circulating antibodies is involved in the development of ITP.[1] In the 1980s it was suggested that ITP may also be attributable to megakaryocyte hypofunction. This was highlighted by the fact that platelet turnover was reduced in a high proportion of ITP patients.[2] Megakaryocytes are found in the bone marrow and are responsible for platelet production. When maturing, megakaryocytes express glycoprotein complexes GPIIb-IIIa and GPIb-IX on their surfaces.[3] In ITP, autoantibodies interact with these complexes, likely having a detrimental effect on the maturing megakaryocyte.[4]

In 1994, the American Society of Haematology (ASH) convened a panel to examine the treatment of idiopathic thrombocytopenic purpura. The outcome of this panel discussion was the practice guidelines, published in 1996.[5] Since then, the findings of a working group in 2008[6] and the ASH evidence-based practice guideline for immune thrombocytopenia (ITP) in 2011 were published. The term 'idiopathic' was removed as ITP is recognised to be an autoimmune disorder, with better understanding than this term would imply. 'Purpura' was removed[6] as bleeding and bleeding symptoms, are not present in all cases.[9]

The diagnosis of ITP continues to be one of exclusion. A diagnosis of ITP is reached in patients with a low platelet count and following elimination of possible secondary causes, for example: exposure to substances, including drugs, vaccines, herbs and foods; lymphoproliferative disorders; infection (including hepatitis C, HIV, cytomegalovirus); bone marrow transplant; and systemic lupus erythematosus (SLE).[8,10] The 2008 working group proposed that the platelet count threshold for the diagnosis of ITP should be $<100 \times 10^9$/l as opposed to the commonly used threshold of $<150 \times 10^9$/l. The rationale for this was the potential ethnic variations in platelet counts. Non-Western

ethnicities have been shown to have lower platelet counts,[11] and counts between 100 and 150x10⁹/l are not uncommon and are asymptomatic.[8] In the 2011 guideline the 100x10⁹/l threshold is adhered to. Treatment is only recommended for patients with counts <30x10⁹/l.[6] Dutch treatment guidelines were published in 2010[7] and can also be found on the website of the Dutch Society of Hematology (www. hematologienederland.nl).

In Europe, the annual ITP incidence is around 3 per 100,000 people.[10] ITP tends to have a higher incidence in middle-aged females and male children.[13] Approximately half of all cases of ITP occur in children;[14] however, the focus of this review is the treatment options for ITP in adults.

METHODOLOGY

For this review the ASH Guidelines, consensus and working group reports[6,8,15,16] were examined along with their reference lists.

A search on PubMed was performed using the terms 'thrombocytopenic', 'purpura', 'therapy', 'treatment', 'therapeutics', 'humans' and 'adult', searching clinical trials, meta-analyses, practice guidelines, randomised controlled trials and reviews. The search was limited to articles in English, published between 1 January 2010 and 1 May 2011.

A search on ClinicalTrials.gov was performed with the search term of 'ITP' among phase II, III and IV trials in adults, thus identifying additional compounds currently in development.

MANAGEMENT OF ADULT ITP

Overview of established treatment

In general, patients with a platelet count below 20,000 to 30,000 10⁹/l should receive treatment. Treatment is rarely started with a higher platelet count.[7,8] The primary first-line treatment is corticosteroids.[7,8] These are recommended for longer courses,[7,8] due to shorter courses being associated with a faster loss of response.[17] Other first-line treatments include anti-Rho(D) immunoglobulins (anti-D) or, if corticosteroids and anti-D are contraindicated or a rapid platelet increase is required, intravenous immunoglobulins (IVIg).[7,8] Splenectomy was recommended as second-line treatment for ITP in the 1996 guidelines[5] and remains so in the 2011 guidelines.[8]

New treatments

Two new compounds have recently been approved for use in the treatment of chronic ITP (second-line treatment) and represent a new class of therapeutic agents. These are

the thrombopoietin receptor (TPO-R, also known as c-Mpl) agonists and thrombopoietic agents.

Thrombopoietin (TPO) is an endogenous growth factor, which directly activates the TPO-R of pluripotent stem cells, thereby stimulating formation of megakaryocyte colony forming units (meg-CFUs).[12,18,19] Activation of the TPO-R induces tyrosine phosphorylation of the Janus tyrosine kinases, Tyk2 and JAK2, and also the signal transducer and activator of transcription 3 (STAT3).[20] This leads to cell proliferation. It has been shown that patients who possess a mutation rendering them unable to produce TPO develop amegakaryocytosis leading to severe thrombocytopenia.[21] The TPO-R is also present on mature megakaryocytes and platelets, suggesting that TPO may also have a direct role in the survival of platelets.

Initial trials with cloned human TPO and similar molecules were unsuccessful.[22] In healthy human volunteers, these molecules were found to be immunogenic, causing the production of antibodies against them. These antibodies in turn acted against the subjects' own endogenous TPO causing thrombocytopenia.[22]

Further trials have focussed on compounds which bear no structural resemblance to endogenous TPO. Therefore, the likelihood of patients producing anti-TPO antibodies is reduced.[23] Romiplostim (a weekly 1 to 10 μg/kg subcutaneous dose) and eltrombopag (a daily 50 to 75 mg oral dose) are the first thrombopoietic agents approved for use in ITP.

Romiplostim

The recombinant Fc-peptide protein romiplostim (EMA approved February 2009) consists of two sections. These include one Fc (antibody) domain which lengthens romiplostim's half-life, and one peptide domain which is the section that binds to TPO-R. Romiplostim binds to the TPO-R as endogenous TPO does and activates the same Tyk2, JAK2 and STAT5 pathways resulting in megakaryopoiesis.[23,24]

In phase III clinical trials in both splenectomised and non-splenectomised patients, romiplostim was found to be well tolerated and effective. The target platelet count (50 to 200x10⁹/l) was achieved within 3 weeks by over half of the patients. Of 125 patients studied, 83 received romiplostim and 42 received placebo. In the treatment arm, a durable platelet response (platelet count ≥50x10⁹/l during ≥6 of the last 8 weeks of treatment) was achieved in 38% of splenectomised patients and 61% of non-splenectomised patients. In the placebo arms, 0% of splenectomised and 5% of non-splenectomised patients achieved a durable response.[12,25]

An additional open-label extension study was conducted for patients who had previously completed a romiplostim trial. As part of an interim analysis, data from 142 patients were

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examined. Of these patients on romiplostim, 30% achieved a platelet response after the first dose and 57% after the third. Over the course of the study a platelet response was achieved in 87% of patients. No response was seen in 13% patients.[26]

The most common adverse event in patients receiving romiplostim in the phase III and extension studies was headache (35% and 37% of patients respectively).[25,26] Fatigue (33%, 30%), epistaxis (32%, 30%), arthralgia (26%, 25%) and contusion (25%, 30%) were the next most frequent.[25,26] The summary of product characteristics (SPC) also states that bone marrow reticulin formation occurred in four of the total 271 patients receiving romiplostim in studies.[27] In one patient who developed bone marrow reticulin formation, a follow-up bone marrow biopsy was carried out 14 weeks after discontinuation which showed improvement in the reticulin deposition.[19]

Eltrombopag

Eltrombopag (EMA approved March 2010) bears significant differences to romiplostim. It is a small, nonpeptide, organic molecule and is described as a TPO nonpeptide mimetic.[23]

Eltrombopag has an additive effect to TPO for which two possible explanations have been suggested. Eltrombopag either directly activates the signalling pathway without involvement of the TPO-R complex, or it binds with the TPO-R at a distance from the TPO binding location. The latter is considered the more likely, with histidine 499 and threonine 496 (in the transmembrane region of the TPO-R) believed to be either the targets or the mediators for binding.[18] The outcome of binding ultimately activates the same signalling pathways as endogenous TPO.[23]

Phase I studies showed that a single dose of eltrombopag was inefficacious. However, after eight days of daily treatment, a dose-dependant increase in platelet count was observed.[28]

A phase III clinical trial was conducted with 118 ITP patients. Splenectomised and non-splenectomised patients were eligible, as were treatment-naive patients and patients receiving concomitant ITP treatment. By day 43, a platelet response (≥50x10^9/l) had been achieved in 81%, 70%, 28% and 11% of patients receiving 75 mg, 50 mg, 30 mg and placebo respectively. Platelet levels in the patients in the 50 and 75 mg groups increased to >200x10^9/l in 37% and 50% of patients, respectively. Eltrombopag was therefore concluded to be an effective short-term treatment.[29]

Another phase III study in 197 patients showed that the median platelet count of patients receiving eltrombopag increased in the first week of treatment from 16 to 36x10^9/l. From day 15 until the end of treatment (6 months) the median platelet count remained between 53 and 73x10^9/l.[29] For patients receiving placebo, platelet counts never increased above 30x10^9/l.[31]

Similar to romiplostim, the most common adverse event with eltrombopag was headache. This was true in both the treatment and placebo groups (21%, 21%, 13% and 10% of patients in the placebo, 75 mg, 50 mg and 30 mg groups, respectively).[28] Headache is listed as the only very common undesirable effect in the eltrombopag SPC.[32] Transient increases in alanine aminotransferase (ALT, 9 patients) and bilirubin (5 patients) concentration were noted in phase III studies.[30] These transient increases were reported to have resolved either during treatment or following discontinuation.[30] However, it is advised that ALT and bilirubin levels are measured before and during treatment with eltrombopag.[32]

ITP REGISTRATION IN THE NETHERLANDS

With the introduction of these new drugs, there are better prospects for the patient with ITP. On the other hand, splenectomy remains an important treatment modality. Insight on long-term data on safety, quality of life and costs is important. With the registration of all patients with chronic ITP, the effects of treatment can be analysed. The ITP working group of the Dutch Society for Hematology developed an ITP registry. The quality of life is measured in collaboration with the Dutch ITP patient's society. Registration started mid 2011 and will continue for five years. Treating physicians are asked to collaborate to include patients into the registry (see www.hematologienederland.nl).

OFF-LABEL TREATMENTS

A number of medications are prescribed off-label to treat ITP with varying degrees of evidence and efficacy. For example, azithioprine, cyclophosphamide, cyclosporine, danazol, dapsone, etoposide, mycophenolate mofetil, procarbazine, rituximab and vincristine have all been investigated as possible ITP therapies. In this review, off-label therapies recommended in the 2011 ASH guidelines[8] and treatments appearing in the PubMed search are summarised.

Rituximab

Rituximab is a chimeric monoclonal antibody currently indicated for CD20 positive diffuse large B cell non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis.[33] Rituximab acts against the CD20 antigen which is found on the surface of B cells.[34] Following administration of rituximab, patients develop depletion of B cells.[35] The depletion of B cells leads to the patient's immune system being unable to produce the anti-GPIIb-IIIa and GPIb-IX antibodies.[34]

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The first prospective, randomised, phase III clinical study of rituximab in ITP compared dexamethasone plus rituximab with dexamethasone alone in 101 treatment-naive patients. An improved sustained response (SR) rate (platelet levels of ≥50x10⁹/l, six months after initial treatment) was seen in the patients in the dexamethasone plus rituximab group compared with dexamethasone (63% vs 36%).[34]

Another study in 62 patients receiving either glucocorticoids plus rituximab or glucocorticoids alone, showed no significant difference in overall response (80.6% and 74.2% respectively), complete response (67.7% and 54.8% respectively) or partial response (12.9% and 19.4% respectively). However, the same study showed that, of the patients who achieved response, SR was achieved in more patients receiving glucocorticoids plus rituximab than glucocorticoids alone (77.4% and 38.7% respectively).[36]

As rituximab is not currently licensed for use in ITP, safety information from the product label would not be pertinent for ITP patients. However, it should be considered that rituximab has immunosuppressant properties and therefore patients may have increased susceptibility to infections. Despite this, rituximab was generally well tolerated in the trials.[34,35] Rituximab is the only off-label therapy recommended in the 2011 ASH guidelines to be considered a second-line therapy.[8]

Mycophenolate mofetil (MMF)

MMF is available as a therapy to avoid rejection in transplant patients. It is also used off-label in a wide range of autoimmune diseases including Crohn's disease, autoimmune myasthenia gravis, rheumatoid arthritis and SLE.[37] MMF acts by inhibition of the enzyme inosine monophosphate dehydrogenase which affects the growth and maturation of lymphocytes, particularly T and B cells.[38] Similar to rituximab, this results in reduction of antibodies against the patients' megakaryocytes and platelets.

Clinical studies have been conducted with MMF and show promising results. In a study of 16 patients, MMF was administered 250 mg twice daily (bid), increased to 500 mg bid after one week and 1 g after two further weeks. A complete response (platelets of >100x10⁹/l) was seen in 55% of patients and a partial response (>50 x10⁹/l) in 45%. MMF showed greater effect in patients with fewer previous treatments.[36] Another study was conducted with 18 'highly refractory' patients (i.e. had failed to respond to other treatment including splenectomy), all of whom received MMF. Of these patients, five showed a good response (>30x10⁹/l) and two showed partial response (no change in platelet count, but less requirement for other treatment).[39] Similar to rituximab, as MMF is not indicated for ITP, the safety data are not fully pertinent to ITP patients.

As with rituximab, MMF is an immunosuppressant and prescribers should be aware of the potential for infection.

Amifostine

Amifostine is a cytoprotective agent. It is currently used to prevent renal toxicity in chemotherapy patients and to prevent xerostomia in patients receiving radiotherapy. Amifostine is inactive until dephosphorylated to its metabolite (WR-1065), which is able to enter cells. WR-1065 exerts a cytoprotective effect by scavenging free radicals, preventing damage to cell membranes and DNA.[40] Furthermore, amifostine has a protective and supportive effect on haematopoiesis and can inhibit apoptosis of haematopoietic cells.[41]

In a clinical trial of amifostine in 24 patients with refractory ITP, all patients showed elevated and stabilised platelet counts. All patients' platelet counts were >100x10⁹/l at the end of treatment (400 mg, 5 times weekly for 4 to 5 weeks), except for two patients with platelet counts of >50x10⁹/l.[41] Another trial in 17 patients demonstrated normal platelet counts in all patients after one course (four weeks) of treatment; all patients' platelet levels remained normal for two months following treatment discontinuation.[43]

Similar to other off-label therapies, amifostine's safety information is not specific to ITP patients. Only moderate adverse events were seen in the studies, including dizziness, nausea, vomiting, fatigue, and mild hypocalcaemia.[41] Of interest was that in patients whose platelet count had been normalised by amifostine and were administered concomitantly with atorvastatin or influenza vaccine, drops in platelet counts were observed.[42]

TREATMENTS UNDER CLINICAL EVALUATION

AKR-501

AKR-501 is a third thrombopoietic agent which is currently in clinical development. Similar to eltrombopag, AKR-501 is a TPO nonpeptide mimetic and acts in a non-competitive manner. AKR-501 has been shown to activate reporter molecules in TPO signalling pathways resulting in growth of megakaryocytes and TPO dependant cells.[19]

A phase II clinical trial using AKR-501 in approximately 65 patients was recently completed (March 2011), the results of which are not yet available.

AS1670542

AS1670542 is another second-generation thrombopoietic, small-molecule TPO agonist. AS1670542 mimics the action of TPO and has shown promising *in vivo* and *in vitro* results.[44]

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Fostamatinib disodium

Currently in phase III clinical development for rheumatoid arthritis and phase II for ITP, fostamatinib disodium is a spleen tyrosine kinase (Syk) inhibitor. It is hypothesised that inhibition of Syk would lead to an amelioration of platelet destruction.[45]

Available phase II trial results show that of the 16 refractory ITP patients enrolled 75% responded to fostamatinib disodium. A sustained response was seen in 50% of patients. Gastrointestinal toxicity (diarrhoea in 6 patients and nausea in 4 patients) was observed, and was attributed to poor specificity of the agent.[45] Further studies are planned to evaluate the safety and efficacy of fostamatinib disodium in ITP patients.

CONCLUSION

Two drugs specific for ITP have recently become available and several established off-label pharmaceutical compounds are being researched for the treatment of ITP. Added to this, a number of molecules are currently in development, specific for the treatment of ITP. This combination of new approved therapies and vibrant research suggests that future prospects of therapy are promising for patients who suffer from ITP.

Physicians are asked to participate in registration of their patients with chronic ITP.

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