Clinical Practice Updates in the Management Of Immune Thrombocytopenia

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INTRODUCTION

Immune thrombocytopenia (ITP), previously called idiopathic thrombocytopenia purpura, is an autoimmune disorder characterized by a severe reduction in peripheral blood platelet count. In healthy individuals, normal platelet count ranges from 150–450 × 10^9/L, while in thrombocytopenia counts fall to less than 100 × 10^9/L.[1] In adults, the incidence of ITP is approximately two to four per 100,000.[2,3] Bleeding risks, specifically hemorrhage and intracranial hemorrhage, represent the most serious complications for patients with ITP. Over the past decade, the understanding of ITP has expanded greatly, which has contributed to a number of updates in the diagnosis and treatment of the disorder.[3] This article aims to briefly review the pathophysiology of ITP and summarize updates in ITP management and treatment options in the adult population.

PATHOPHYSIOLOGY

Two major mechanisms contribute to the development of ITP: increased platelet destruction and insufficient platelet production.[4] Platelet destruction, the most common mechanism of ITP development, involves loss of self-tolerance of platelet antigens and formation of antibodies that target glycoprotein IIa/IIIa on platelets, causing their destruction by macrophages or cytotoxic T cells.[5,6] Impaired function of megakaryocytes and an insufficient level of thrombopoietin (TPO) are two factors involved in decreased platelet production.[5,6] Normally, new platelets are formed daily from megakaryocytes, and TPO is the main regulator of this process.

ITP can be classified as primary (idiopathic) or secondary. Primary ITP is a diagnosis of exclusion that constitutes about 80% of diagnosed patients.[7] Thrombocytopenia from secondary causes can vary based on the presence of trigger factors, such as certain drugs, autoimmune diseases, viral infections, or vaccinations (Table 1).[8–10] Typically, treatment of secondary ITP focuses on resolving the underlying cause or disorder, as well as reducing platelet destruction and stimulating platelet production.

TERMINOLOGY

Previously, limited clinical and laboratory parameters were available to define and classify ITP. This contributed to a lack of standardized definitions and terminology in the classification of the disorder. Over the last decade, significant standardization has been recommended that has allowed for alignment of research studies and guidance in the management of patients with ITP. An international ITP working group removed the term "acute ITP" because this diagnosis can only be made retrospectively after a patient's platelet count has recovered. Instead, the working group proposed the terms "newly diagnosed ITP" for the phase of the first three months post-diagnosis, "persistent ITP" referring to symptoms lasting between three and 12 months, and "chronic ITP" to include patients with consistent thrombocytopenia lasting longer than 12 months. In addition, descriptive terminology was proposed for patients meeting severe and refractory criteria, as well as what would define a response in therapy (Table 2).[2,11,12]

ADULT TREATMENT PRINCIPLES

Due to higher morbidity and mortality in patients with platelet counts of less than 20–30 × 10^9/L, clinical guidelines recommend initiating treatment once platelet counts fall below 30 × 10^9/L or at any platelet level when clinically significant hemorrhage is present.[11,12] Therapy should be tailored to patients based upon presence of bleeding, desired platelet count increase, lifestyle that may predispose patients to trauma, side effects of therapy, and patient preferences.[9] Over the past decade, significant advances have been made in ITP management. With guidelines lagging behind clinical practice, a review of current therapeutic options and clinical practice is beneficial in further clarifying ITP management.

FIRST-LINE THERAPIES

Corticosteroids remain the mainstay of initial management of ITP. Intravenous immunoglobulin (IVIG) and anti-D immune globulin (in patients who have an Rh-positive blood type) have also been recommended as first-line treatment options. These agents are used to recover platelet count quickly in emergent situations and are not intended for long-term therapy because of limited duration of response and long-term toxicity.[13] Corticosteroids are usually the first choice for initial treatment of ITP due to ease of administration and lower cost. However, IVIG can increase platelet count more rapidly and may be preferred in patients with active bleeding. Table 3 provides a summary of first-line treatments to be discussed.

Corticosteroids

In the management of ITP, corticosteroids act by reducing antibody production and preventing platelet destruction by macrophages. Available corticosteroids include prednisone, prednisolone, methylprednisolone, and dexamethasone. The most common regimens are oral prednisone 0.5–2.0 mg/kg

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Table 1 Causes of Secondary Immune Thrombocytopenia[8–10]

Autoimmune Disorders	Infections	Drugs	Vaccinations
• Systemic lupus erythematosus • Antiphospholipid syndrome	• Human immunodeficiency virus • Hepatitis C virus • *Helicobacter pylori*	• Heparin • Penicillin • Nonsteroidal anti-inflammatory drugs	• Measles • Mumps • Rubella • Varicella

Table 2 International Working Group Descriptive Terminology for ITP[2,11,12]

Terminology	Description
Newly diagnosed	Less than three months duration of thrombocytopenia
Persistent	Three to 12 months duration of thrombocytopenia
Chronic	More than 12 months duration of thrombocytopenia
Severe	Significant bleeding requiring treatment, additional interventions, or an increase in drug dose
Refractory	Persistence of severe ITP after splenectomy
Response	Platelet count ≥ 30 x 10^9/L and a greater than twofold increase in platelet count from baseline measured on two occasions (more than seven days apart)
Complete response	Platelet count ≥ 100 x 10^9/L measured on two occasions (more than seven days apart)

ITP = immune thrombocytopenia.

per day for two to four weeks followed by a gradual taper, or an intensified steroid regimen of dexamethasone 40 mg per day for four days every two to four weeks for one to four cycles with no taper.[13,14] A recent multicenter, randomized study compared the efficacy and safety of high-dose dexamethasone and prednisone for treatment of patients with newly diagnosed ITP.[14] Patients were randomized to receive either dexamethasone 40 mg per day for four days (with nonresponders receiving an additional four-day treatment) or prednisone 1 mg/kg per day for four weeks. The primary endpoints were initial response (defined as platelet count greater than 30 × 10^9/L) and sustained response (platelet count greater than 30 × 10^9/L for six consecutive months). Dexamethasone resulted in greater overall initial response (82.1% versus 69.1%; $P = 0.044$); a higher rate of complete response, defined as a platelet count greater than 100 × 10^9/L (50.5% versus 26.8%; $P = 0.001$); and a shorter time to response. Sustained response was similar in both groups (40% for dexamethasone versus 41.2% for prednisone; $P = 0.88$).[14]

A meta-analysis of nine randomized trials published between 2004 and 2015 observed an overall superior platelet count response at two weeks of therapy in patients taking dexamethasone compared with those taking prednisone (79% versus 59%; $P = 0.048$) and fewer adverse events (24% versus 46%).[15] The improved tolerability and fewer adverse effects observed with dexamethasone may potentially have been due to an overall shorter duration of therapy. Overall, sustained platelet response rates are similar between dexamethasone and prednisone, and each should be considered as a first-line agent in the management of ITP. High-dose dexamethasone may be considered in specific situations when a higher early response rate is warranted.

Use of long-term corticosteroids should be avoided when possible due to significant adverse effects, such as osteoporosis, diabetes, hypertension, and weight gain.[16] For patients who do not maintain a stable platelet count after initial therapy with corticosteroids, IVIG therapy can be considered until a second-line treatment option may be given. This same principle can be considered in patients unable to tolerate the adverse effects of corticosteroids.

Intravenous Immunoglobulin G

IVIG is derived from pooled plasma of human donors and is thought to saturate Fc receptors in the reticuloendothelial system, leading to decreased destruction of platelets that have bound autoantibodies. It was initially shown to be effective in the treatment of ITP in the 1980s.[7]

Current dosing guidelines recommend administration of 1 mg/kg IVIG as a single dose, repeated as necessary based upon platelet response.[9] An increase in platelet count is typically expected within 24 to 48 hours in up to 85% of patients.[17] However, response may be transient, lasting no longer than three to four weeks—prompting additional therapy once platelet counts fall below 30 × 10^9/L. The efficacy of different IVIG doses was studied in a randomized, multicenter trial to establish the optimal IVIG dose for adults with ITP.[18] The study showed that the 1 g/kg dosing method resulted in a faster platelet response rate than the 0.5 g/kg regimen (day 4 rate of response, 67% versus 24%, respectively; $P = 0.01$). The overall increase in platelet count was significantly greater in the higher-dose group compared with the lower-dose group (106 × 10^9/L versus 55 × 10^9/L; $P = 0.03$). Nonresponders received additional IVIG doses for a total dose of 2 g/kg, which resulted in a response rate of 78% in the entire study group. These results support IVIG reinfusion if no response is observed on day 3 of therapy.

Health care professionals and patients should be aware of the precautions surrounding IVIG administration. Infusion-related IVIG reactions are usually dependent upon the rate of infusion and/or the specific product. Products are not clinically interchangeable due to numerous differences such as osmolality, immunoglobulin A content, and different stabilizers (sucrose, glucose, maltose). When administered according to the prescribing information, IVIG is generally well tolerated, with the most common side effects being headaches, chills, arthralgia, and back pain. Serious complications, specifically thrombotic events, are rarely observed.[19] A 2016 systematic review and meta-analysis of randomized controlled studies found no evidence of increased thromboembolic events compared with the control group.[19] Of note, renal impairment has been reported with some sucrose-containing IVIG formulations.[17,19] Adequate hydration prior to administration can help alleviate the risk of acute kidney injury with these formulations.

Table 3 First-Line Treatment Options for Immune Thrombocytopenia[9,13,14,21,22]

Dose	Initial Response/ Peak Response	Response Rate	Adverse Effects	Comments	Average Wholesale Price[58]
Prednisone (Mylan Pharmaceuticals, Inc.)[a]					
0.5–2.0 mg/kg daily for 3–4 weeks	4–14 days/ 7–28 days	70–80%	Insomnia, hypertension, hyperglycemia, mood disorders, weight gain, dizziness, edema	Requires dose tapering	$22.40 for 100 20-mg tablets
Dexamethasone (Par Pharmaceutical)[a]					
40 mg daily for 4 consecutive days every 2–4 weeks, 1–4 cycles	2–14 days/ 4–28 days	Up to 90%	Same as prednisone, but less frequent	Faster onset of action than prednisone	$98.85 for 100 6-mg tablets
Intravenous Immune Globulin (Gammagard liquid, Baxalta, Inc.)[b]					
1 g/kg daily for 1–2 days	1–3 days/ 2–7 days	Up to 85%	Infusion-related reactions, nephrotoxicity	First-line if corticosteroids are contraindicated or produce suboptimal response	$783.80 for 50-mL vial (100 mg/1 mL)
Anti-D Immune Globulin (WinRho SDF, Aptevo Biotherapeutics LLC)[b]					
50–75 mcg/kg	1–3 days/ 3–7 days	70–80%	Hemolysis	Only in D-positive patients; monitor patients for 8 hours after administration	$514.35 for 1.3-mL vial (300 mcg)

[a] Cost represents lowest average wholesale price for generic drug available at the time of writing.
[b] Representative product commonly used in clinical practice.

Anti-D Immune Globulin

Anti-D immune globulin was approved by the Food and Drug Administration (FDA) for the treatment of immune thrombocytopenia in nonsplenectomized Rh-positive patients in 1995.[20] Prepared from the plasma of immunized Rh-negative human donors, it can be used as an alternative to conventional IVIG for patients who have an Rh-positive blood type. By acting against the D antigen, this treatment blocks the macrophage system, neutralizing binding of autoantibodies to platelets.[20] Initial dosing recommendations range from 50–75 mcg/kg intraveneously.[21,22] A prospective, randomized trial compared the treatment of ITP with the approved dose of 50 mcg/kg to the higher dose of 75 mcg/kg.[22] The higher dosing regimen resulted in a greater platelet rise on day 1 (43×10^9/L versus 7.5×10^9/L; $P = 0.012$) and day 7 (153×10^9/L versus 64.5×10^9/L; $P = 0.001$). In addition, the duration of response was longer with the 75 mcg/kg dosing regimen (46 days versus 21 days; $P = 0.03$). This dose-related response with the use of anti-D immune globulin in the treatment of ITP has moved many institutions to begin with 75 mg/kg instead of the lower dose.

Adverse events experienced with anti-D immune globulin treatment are similar to conventional IVIG and include headache, fever, chills, nausea, and vomiting. Fatal intravascular hemolysis (IVH) and multiorgan dysfunction have been also reported and are listed as boxed warnings.[23] Due to the severity of these adverse effects, patients receiving anti-D immune globulin should be monitored for at least eight hours after administration for signs and symptoms of IVH, including fever, chills, back pain, discolored urine, and anemia.[20]

In comparison with IVIG, the advantages of anti-D immune globulin include lower cost and shorter time of administration (minutes versus hours), which can translate to significant cost-savings. Kumar et al. reviewed records of 186 children with ITP to determine the cost of treatment with anti-D immune globulin compared with IVIG and found the cost of anti-D immune globulin was $1,512 versus $2,245 for IVIG calculated for a hypothetical 20-kg child.[24] Patients in the IVIG group also incurred more hospital charges associated with drug administration. Institution-specific analysis comparing cost of treatments is recommended to determine overall cost-savings.

SECOND- AND THIRD-LINE THERAPIES

Second- and third-line ITP treatments are typically reserved for patients with persistent and chronic ITP not requiring emergent or rescue treatment. Current guidelines recommend splenectomy and rituximab as second-line treatment options, while in clinical practice the emergence of novel treatment options has pushed splenectomy to a third-line status.[2,9,25] Although splenectomy remains an effective treatment option in appropriate patients when other options have failed, emerging clinical data on the use of TPO receptor agonists (TPO-RAs), including eltromobopag (Promacta, Novartis) and romiplastim (Nplate, Amgen), have shown effective results, leading to a reduction in splenectomy rates.[26]

It has also been established that second- and third-line treatments may be used in combination with steroids or other immunosuppressive agents.[12,27,28] Combination therapies may be useful in patients who are refractory to monotherapies and

Table 4 Second- and Third-Line Treatment Options for ITP[37,44,45]

Dose	Initial Response/ Peak Response	Response Rate	Adverse Effects	Comments	Cost
Splenectomy					
NA	1–56 days/ 7–56 days	60–80%	Bleeding, increased risk of infections, thrombotic events	Effective; consider after multiple treatment failures	$25,262[57]
Rituximab (Rituxan, Genentech)					
375 mg/m^2 IV over 4 hours once weekly for 4 consecutive weeks	7–56 days/ 14–180 days	60%	Infusion reactions, neutropenia, fever, infections, asthenia	Second-line therapy option	AWP $1,042.40 for 10-mL vial (10 mg/mL)[58]
Eltrombopag (Promacta, Novartis)					
50–75 mg daily	7–28 days/ 14–90 days	80%	Hepatotoxicity, thrombotic events	Second- or third-line option if treatment failure occurs	AWP $9,013.60 for 30 50-mg tablets[58]
Romiplostim (Nplate, Amgen)					
1 mcg/kg SC once weekly	14–21 days/ not reported	79–88%	Arthralgia, thrombocytopenia, thrombotic events	Second- or third-line option if treatment failure occurs	AWP $2,064.20 for 250-mcg vial (powder for solution)[58]

AWP = average wholesale price; ITP = immune thrombocytopenia; IV = intravenous; NA = not applicable; SC = subcutaneous.

may result in an enhanced response because they target multiple mechanisms. Table 4 provides a summary of second- and third-line treatment options.

Splenectomy

Splenectomy was historically the gold-standard treatment for severe chronic ITP prior to the introduction of steroids more than 60 years ago.[29,30] Advances in the understanding of ITP over the past decade that led to the advent of more treatment regimens have since relegated splenectomy to a third-line treatment option in clinical practice. Current guidelines suggest splenectomy may be considered for patients with ITP who have, at minimum, failed corticosteroid therapy.[9] Those undergoing splenectomy have shown a 60% to 80% response rate, with remission in about two-thirds of these patients.[13,29,30] Interestingly, higher response rates have been observed in younger patients.[29] A European study published in 2016 reported that younger patients who had higher preoperative and postoperative peak platelet counts, later peak platelet count emergence times, and higher megakaryocytes at diagnosis were more likely to respond to splenectomy.[31] Platelet kinetic parameters and scintigraphic indices, specifically spleen/liver at 30 minutes, have also been studied and are useful in predicting the success of splenectomy.[32]

A major limiting factor in deciding on splenectomy in patients with ITP is bleeding associated with the surgical procedure. Mortality rates of 0.2% and 1.0% with laparoscopy and open laparotomy, respectively, have been reported and associated with postoperative bleeding complications.[30] These rates, based on a systematic review of case series, raise concern that the risk of death from having a splenectomy is potentially greater than that of having thrombocytopenia itself. Additional surgical complications limiting this management option include venous thromboembolism, pneumonia, and other infections.[29,30] Immunization (pneumococcal, meningococcal, and *haemophilus influenzae* type b) should be considered for patients undergoing an elective splenectomy to protect against encapsulated bacterial pathogens and to decrease the incidence of post-splenectomy sepsis.[33]

Overall, splenectomy provides an effective treatment option for ITP, but it is limited by the risk of surgical complications. The risk of these complications versus the benefit of an increased platelet count should be considered. While certain patient factors can help predict positive response rates, no specific recommendations for indications or timing of splenectomy in patients with ITP have been determined.

Rituximab

Rituximab (Rituxan, Genentech), an anti-CD20-directed cytolytic monoclonal antibody, works by inhibiting B cells from producing autoantibodies as well as reverting T-cell abnormalities in patients who respond to treatment.[34–36] It received FDA approval for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis (RA) in combination with methotrexate in adults with moderately to severely active RA.[37] However, despite lack of evidence from randomized controlled trials, rituximab is used off-label for the treatment of adults with ITP.[9,13,38] Rituximab is reserved for patients with a high bleeding risk who have failed treatment with at least IVIG, anti-D immune globulin, or corticosteroids.

Efficacy studies on rituximab and IVIG have shown promising results. A systematic review of literature on the efficacy and safety of rituximab for the treatment of adults with ITP reported 60% of patients with chronic disease had a platelet response defined as greater than 50×10^9/L.[37] The review suggests that rituximab may reduce the number of patients who sustain thrombocytopenia in chronic ITP. Use of rituximab has also been shown to improve relapse-free survival if administered early; however, optimal timing has yet to be determined.

Major short-term adverse effects of rituximab include pruritus, urticaria, chills, vomiting, fever, and serum sickness.[37,39,40] Premedication with an antihistamine and antipyretic may be administered 30 minutes prior to starting a rituximab infusion to prevent some of the short-term infusion-related adverse effects.[40] In addition, adequate hydration and the monitoring of electrolytes and renal function are recommended.[37] In order to alleviate the incidence of infusion-related side effects, many institutions utilize protocols that automatically prompt providers to consider premedications in patients receiving rituximab. Long-term side effects have also been observed. In patients being treated for more than 12 months, use has been associated with infections, malignancies, pulmonary embolism, pneumonitis, and central nervous system hemorrhage.[38] It should be noted, however, that direct correlation between these long-term adverse effects and rituximab use alone has yet to be determined.

Similar to splenectomy response indicators, predictors have been identified for rituximab use. Female gender, age younger than 40 years, and shorter period between diagnosis and rituximab administration have all been associated with good response outcomes.[41–43] A retrospective analysis of 103 patients with primary ITP who were treated with rituximab reported that patients younger than 40 years of age and women had a significantly higher probability of achieving a platelet count of at least 100×10^9/L.[42]

Although it is not FDA approved for the treatment of ITP, dosing recommendations for rituximab in ITP have been determined. The most common dose is 375 mg/m^2 administered once weekly for four consecutive weeks.[38,39,42] To reduce the incidence of infusion-related reactions, rituximab is typically administered over an extended infusion of four hours. An initial response can be expected within seven to 56 days, with an average of about 38 days.[9] Although it is an effective treatment option, with this wide range of response time, the role of rituximab for emergent treatment or in an acute setting is limited.

Thrombopoietin Receptor Agonists

The TPO-RAs eltrombopag and romiplostim have been approved by the FDA for patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.[44,45] TPO-RAs work by activating TPO receptors on megakaryocytes and inducing platelet production via the JAK2 and STAT5 kinase pathways.[7,36] At the time of the last guideline publication in 2011, limited long-term safety and efficacy data were available on TPO-RAs. Since that time, however, research and clinical utilization of eltrombopag and romiplastim have changed the clinical landscape of ITP treatment and management.

Eltrombopag

Eltrombopag was evaluated in a double-blind, randomized, controlled trial that assessed its efficacy and safety in 118 adults with chronic ITP and platelet counts of 30×10^9/L who had relapsed or whose platelet count was refractory to at least one standard ITP treatment.[46] Patients were randomly assigned to receive eltrombopag 30 mg, 50 mg, or 75 mg once daily or placebo for up to six weeks. The primary endpoint, defined as a platelet count of 50×10^9/L or greater on day 43, was achieved in 11% of patients receiving placebo and 28%, 70%, and 81% of patients receiving 30 mg, 50 mg, and 75 mg per day of eltrombopag, respectively ($P < 0.001$ in the 50-mg and 75-mg groups). An increase in platelet count to at least 200×10^9/L in 14%, 37%, and 50% of patients receiving 30 mg, 50 mg, and 75 mg, respectively, and 4% patients receiving placebo was observed. The results of this study suggest a dose-dependent platelet rise with the use of eltrombopag. The most common adverse event reported was headache, which was similar in all groups.[46] The long-term EXTEND trial has published data for a three-year follow-up in an extension study of extended dosing of eltrombopag in patients with chronic ITP.[47] The study showed positive overall response rates, with 85% of patients with median platelet counts increasing to greater than 50×10^9/L by week 2 of treatment and remaining increased for the duration of the study. For half of the study duration, 62% of patients had sustained platelet counts of 50×10^9/L or greater.[47] The most common adverse events reported were mild, including headache, nasopharyngitis, upper respiratory infection, and fatigue. An update to the study recently presented at an American Society of Hematology meeting reported that the most common grade 3 or higher adverse effects included elevation of hepatic enzymes in 15% of patients and thromboembolic events in 6.3% of patients at year 5 of the study.[2]

Results of this study demonstrated the efficacy of eltrombopag in increasing and maintaining platelet counts for up to three years. Current dosing guidelines recommend an eltrombopag starting dose of 50 mg once daily in adults. In pharmacokinetic studies, plasma eltrombopag exposure was significantly higher in some patients of East Asian ancestry (including Chinese, Japanese, Taiwanese, and Korean heritage) and those with hepatic insufficiency. Thus, a reduced dose of 25 mg once daily is recommended in patients of East Asian descent or patients with moderate-to-severe hepatic insufficiency.[9,44] Doses may be titrated in increments of 25 mg until a platelet response of at least 50×10^9/L is achieved. Considering eltrombopag's pharmacokinetic profile, obtaining a complete blood cell count (CBC) with differential is recommended weekly until a platelet response of at least 50×10^9/L is achieved and monthly thereafter while on therapy. Due to eltrombopag's known effect on liver function, hematology and liver enzymes should also be monitored throughout therapy.

Romiplostim

Romiplostim, another TPO-RA currently on the market, was evaluated in a double-blind, randomized, controlled trial assessing the efficacy of long-term administration in splenectomized and nonsplenectomized patients with ITP.[48] Participants were randomly assigned to receive subcutaneous injections of romiplostim (splenectomized, n = 42; nonsplenectomized, n = 41) or placebo (splenectomized, n = 21; nonsplenectomized, n = 21) every week for 24 weeks. Baseline platelet counts in both treatment groups were similar. A durable treatment response (defined as a platelet count of 50×10^9/L during six or more of the last eight weeks of treatment) was achieved in 16 of 42 patients (difference in proportion of patients responding, 38%; 95% confidence interval [CI], 23.4–52.8; $P = 0.0013$) in the splenectomized group and in 25 of 41 patients (difference

in proportion of patients responding, 56%; 95% CI, 38.7–73.7; $P < 0.001$) in the nonsplenectomized group. Overall platelet response (defined as either durable platelet response or four or more weekly responses of 50×10^9/L any time during the study) was achieved in 88% of patients receiving romiplostim in the nonsplenectomized group and 79% in the splenectomized group ($P < 0.0001$). The most common adverse effects reported were similar in each study group and consisted of headache, fatigue, epistaxis, and arthralgia. Two serious adverse events reported were bone marrow reticulin formation, which resolved with discontinuation of romiplostim, and thromboembolism in a patient with previous history of vascular disease with platelets above baseline but below normal range.[48] A separate study evaluating bleeding and thrombotic events during long-term use of romiplostim reported a decreased incidence and severity of bleeding and no difference in the incidence of thrombotic events in patients with chronic ITP receiving romiplostim compared with placebo.[49]

A larger analysis by Cines et al. reviewed more than 900 patients treated with romiplostim in 13 clinical trials.[50] Participants were evaluated over a study period of 55 to 75 weeks; common romiplostim dosing was 5 mcg/kg and 4.6 mcg/kg (splenectomized and nonsplenectomized patients, respectively). Similar to previous studies, the most frequent adverse effects were headache, epistaxis, and nasopharyngitis. A similar incidence of thromboembolism was observed between treatment and placebo groups.[50] Bone marrow reticulin fiber formation was approximately 3% for romiplostim, with higher rates and severity in patients receiving doses greater than 10 mcg/kg.[50]

The results of these studies suggest that romiplostim can be used effectively to manage chronic ITP regardless of whether patients have undergone splenectomy. Adverse effects are mild, and evidence to support a significantly increased risk of thromboembolic events is lacking. Current dosing recommendations support a starting dose of 1 mcg/kg once weekly based on body weight.[45,46] Doses may be adjusted by 1 mcg/kg per week (to a maximum of 10 mcg/kg per week) to achieve a platelet count of at least 50×10^9/L. The response is not immediate; an initial response may take four to nine days. CBCs should be monitored weekly until a platelet count of at least 50×10^9/L is achieved and monthly thereafter during treatment.

Other Immunosuppressive Agents

In patients presenting with chronic refractory ITP, limited studies have shown a potential benefit with the use of immunosuppressive agents.[51–57] These immunosuppressive agents, including mycophenolate, azathioprine, and cyclosporine, may be used alone or in combination for the treatment of ITP. In one retrospective, observational study of 19 patients with refractory ITP who had previously failed a median of six prior treatments, including splenectomy, treatment with mycophenolate, azathioprine, and cyclosporine combinations was reviewed. Fourteen patients responded to treatment for a median of 24 months, with eight subsequently relapsing. Severe adverse effects were not observed during the study period. Combination immunosuppressant therapy can produce a rise in the platelet count that is sometimes sustained in refractory ITP patients.

ECONOMIC CONSIDERATIONS

With multiple agents demonstrating significant safety and efficacy outcomes and with the advent of novel agents to the market, financial implications for each agent should be considered. See Tables 3 and 4 for cost estimations. A limited number of studies have investigated the cost associated with ITP management and pharmacological treatment. One recent study examined length of hospital stay, hospitalization cost, and risk of in-hospital mortality among adults with ITP.[57] The investigators estimated 296,870 patient discharges between 2006 and 2012 were associated with ITP. The average length of stay for these patients was six days, which was higher than that of the overall U.S. discharge population. In addition, the average cost of ITP hospitalization was 48% higher than the overall cost of the U.S. discharge population. As expected, the longest length of stay and the highest cost were for those who had a splenectomy or experienced septicemia secondary to ITP treatment. The highest mortality prevalence was associated with septicemia and intracranial hemorrhage. Elderly patients were found to be most vulnerable to ITP-related hospitalizations.[57]

Treatment of ITP may require therapies that vary by type, duration (onset of action and peak effect), and cost. In fact, multiple treatment modalities may be needed to safely and effectively manage the disease state. Evaluating all these factors when formulating a treatment plan for patients can potentially lower the cost associated with ITP hospitalizations.

CONCLUSION

Recent studies and updates in the literature have added much to what we know about the pathophysiology of ITP and how to translate this knowledge into clinical practice and treatment guidelines. Novel therapies have provided alternatives to splenectomy and have been shown to be effective in managing ITP with few adverse effects. In selecting treatment options, therapy should be individualized to each patient to account for bleeding risk, age, and lifestyle. First-line emergent treatments include corticosteroids, IVIG, and anti-D immune globulin. For patients presenting with ITP that is not life threatening, corticosteroids are considered the standard initial treatment due to their effectiveness, low cost, and convenience. IVIG is recommended for patients with critical bleeding and for those unresponsive to corticosteroids. The alternative option is anti-D immune globulin, which can be used in nonsplenectomized Rh-positive patients. Second- and third-line treatment options for nonemergent and chronic ITP have historically included only splenectomy or rituximab. Rituximab is an off-label treatment for ITP reserved for patients who do not respond to corticosteroids. Splenectomy is a potentially curative treatment that is used when multiple first-line treatments have failed. The arrival of TPO-RAs to the market has provided an additional option for chronic ITP management and has greatly changed the ITP treatment landscape. While the role of TPO-RAs is likely to evolve with continued clinical safety and efficacy data, research and clinical use to date have shown encouraging results. In selecting treatment regimens in the management of ITP, it is important to evaluate the type, duration, and cost of these treatments because patients may face longer hospital stays, increased risk of mortality, and increased costs for ITP-related hospitalizations.

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