REVIEW ARTICLE

blood advances

Management of newly diagnosed immune thrombocytopenia: can we change outcomes?

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Immune thrombocytopenia resulting from antibody-mediated platelet destruction combined with impaired platelet production is a common cause of thrombocytopenia. The decision to treat newly diagnosed patients is based on several factors including ceasing hemorrhagic manifestations, increasing the platelet count, prevention of bleeding, and inducing remission. Current standard first-line therapy is a course of corticosteroids. Although this treatment paradigm increases the platelet count in the majority of patients, a high percentage relapse after discontinuation of corticosteroid therapy. For this reason, intensification of first-line therapy that results in superior long-term remission rates would be desirable. This manuscript focuses primarily on adults with idiopathic thrombocytopenic purpura (ITP), highlighting pediatric data and practice when applicable. The primary aim is to outline upfront strategies for treatment-naive patients with ITP to enhance remission rates, taking into account assessment of the risks and benefits of these approaches.

Introduction

Immune thrombocytopenia (ITP) resulting from increased antibody-mediated platelet clearance and impaired platelet production occurs in ~1.9-6.4 per 100 000 children per year and 3.3 per 100 000 adults per year.[1] At the time of diagnosis, treatment may be aimed at immediate and rapid control of life-threatening hemorrhage or reducing mucosal bleeding symptoms. Fortunately, life-threatening or severe bleeding is a rare event,[2] with ~9.6% and 20.2% of adults and children, respectively, experiencing major hemorrhage. Because significant bleeding is uncommon at presentation, a standard goal of therapy is to increase the platelet count to prevent subsequent hemorrhage. Although the link between thrombocytopenia and bleeding is well established, there is no clear evidence of a direct correlation between the degree of thrombocytopenia and bleeding symptoms, especially at lower platelet counts. Thus, bleeding in ITP is heterogeneous, unpredictable, and likely based on a composite of risk factors.[2,3] Because of this, no evidence-based validated risk stratification model for treatment exists.

A final rationale for upfront therapy in an asymptomatic patient is the prevention of chronic or relapsing disease by way of exposure to immunomodulatory therapy. In children with ITP, this rationale is less applicable, as children tend to have high spontaneous remission rates and low likelihood of disease recurrence or chronicity. In adult patients, however, relapse is common after treatment with corticosteroids. Approximately 50% of patients have relapsed by 6 months, with an additional 25% relapsing beyond 1 year.[4] Therefore, new strategies to further induce remission rates, defined as a platelet count $\geq 100 \times 10^9$/L,[5] in this population would be desirable.

This article reviews indications for therapy in patients with newly diagnosed ITP and addresses current areas of investigation and controversy with regard to initial management.

Submitted 21 August 2017; accepted 29 August 2017. DOI 10.1182/bloodadvances.2017009860.

This article was selected by the *Blood Advances* and *Hematology 2017 American Society of Hematology Education Program* editors for concurrent submission to *Blood Advances* and *Hematology 2017*. It is reprinted in *Hematology Am Soc Hematol Educ Program*. 2017;2017:400-405.

Table 1. American Society of Hematology Guidelines for the Management of Newly Diagnosed ITP in Adults and Children (adapted from the American Society of Hematology Guidelines for Immune Thrombocytopenia[5])

Children
We recommend:
• Children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) be managed with observation alone regardless of platelet count (grade 1B);
• In pediatric patients requiring treatment, a single dose of IVIg (0.8-1.0) or a short course of steroids be used as first-line treatment (grade 1B);
• IVIg can be used if a more rapid increase in the platelet count is required (grade 1B);
• Anti-D immunoglobulin therapy is not advised in children with a hemoglobin concentration that is decreased due to bleeding or with evidence of autoimmune hemolysis (grade 1C).
We suggest:
• A single dose of anti-D immunoglobulin can be used as first-line treatment in Rh-positive, nonsplectomized children requiring treatment (grade 2B).
Adults
We suggest:
• Treatment be administered to for newly diagnosed patients with a platelet count $<30 \times 10^9$/l (grade 2C);
• Longer courses of steroids are preferred over shorter courses of corticosteroids or IVIg as first-line treatment (grade 2B);
• IVIg can be used with corticosteroids when a more rapid increase in the platelet count is required (grade 2B);
• Either IVIg or anti-D immunoglobulin (in appropriate patients) be used as first-line treatment if corticosteroids are contraindicated (grade 2C);
• If IVIg is used, the dose should be initially 1 gm/kg as a 1-time dose; this dosage may be repeated if necessary (grade 2B).

Determining whom to treat

In patients who present with ITP, the platelet count is frequently used as a surrogate marker for disease severity, and thus often determines the need for therapy. The 2011 American Society of Hematology (ASH) evidence-based practice guidelines on ITP made recommendations regarding the initial management of newly diagnosed adults and children (Table 1).[6] These recommendations are also highlighted in the ASH "Choosing Wisely" campaign.[7]

Children

For children with newly diagnosed ITP and no or mild bleeding at diagnosis, defined as skin manifestations only, treatment is not indicated regardless of platelet count. This is supported by data from a large registry showing that of 505 children who had no or mild bleeding (skin manifestations only) at diagnosis with platelet counts $<20 \times 10^9$/L, only 3 (0.6%) developed more significant bleeding in the subsequent 28 days, and none experienced intracranial hemorrhage.[8] There was no relationship between initial management and development of significant hemorrhage ($P = .82$). This recommendation is consistent with recommendations from a consensus report.[9]

Adults

For adults with newly diagnosed ITP and platelet count $<30 \times 10^9$/L, treatment is suggested by the guidelines even in the absence of mucosal bleeding symptoms.[6] This recommendation is not evidence-based, and the acceptable platelet count threshold for treatment remains unknown. A model estimating bleeding risk predicted that patients with a platelet count $<30 \times 10^9$/L and older age were at higher risk for bleeding.[10] However, there were inherent flaws in that model, such as the underlying dataset used, lack of thresholds besides 30×10^9/L, and large confidence intervals. Because of these limitations, these data were not assimilated into the final recommendation for treatment. The international consensus report does not specify a lower limit threshold but does state that the majority of asymptomatic adults with a platelet count $>50 \times 10^9$/L should not require treatment.[9]

Additional considerations for treatment include the need for upcoming medical procedures, concomitant antithrombotic therapy or other comorbidities with a bleeding risk, and improved overall health-related quality of life. Clearly, validated risk stratification models based on platelet count and additional patient-related factors would aid in decision-making.

Standard first-line treatment

Available first-line therapy for both adults and children includes oral corticosteroids, intravenous immunoglobulin (IVIg), and anti-D immunoglobulin (Table 2). IVIg and anti-D immunoglobulin have the benefit of inducing a more rapid increase in platelet count than oral corticosteroids, but they also require intravenous infusion and usually demonstrate a more transient response.[9] The risk-benefit profile of the medications must be carefully weighed. Common side effects, outlined in Table 1, for IVIg and anti-D immunoglobulin tend to be more transient than those of corticosteroids; however, they can be severe. For these reasons, oral corticosteroids are the preferred choice for first-line therapy unless there is a contraindication to corticosteroids or a need for more prompt increase in the platelet count such as life-threatening hemorrhage.[6] The traditional dose for adults is prednisone (1-2 mg/kg per day) over several weeks with a taper. Initial response rates with this approach range from 70% to 80%; however, high relapse rates result in low long-term remission rates.[9] In children, a shorter course of corticosteroids (2-4 mg/kg per day for 5-7 days) is chosen given the unfavorable side effects of ongoing corticosteroid use and the likelihood of spontaneous recovery within days to weeks of diagnosis.

Optimizing corticosteroid therapy

Recently, data have emerged on shorter courses of high-dose steroids such as dexamethasone. The rationale for dexamethasone use is based on the ability to provide an equivalent amount of corticosteroid therapy but with a shorter exposure period. Standard dosing is 40 mg daily for 4 days, with courses repeated monthly based on platelet count.

Table 2. Standard first-line therapy for ITP

Therapy and dose	Dose	Time to response	Prominent side effects
Corticosteroids		3-4 d	Mood changes, hypertension, hyperglycemia, gastritis
Adults	Prednisone 1-2 mg/kg per day with taper		
	Dexamethasone 40 mg/d × 4 days for 1-3 cycles		
Children	2-4 mg/kg orally divided two times a day for 5-7 days		
IVIg	0.8-1.0 g/kg IV for one dose	24-48 h	Infusion reaction, headache, aseptic meningitis, thrombosis
Anti-D immunoglobulin	50-75 μg/kg IV for one dose	24-48 h	Hemolysis (2.0 g decrease in hemoglobin), FDA black box warning

At the time of guideline and consensus report development, only single-arm data on dexamethasone had been published, which limited the recommendation on corticosteroid choice.[6,9] Since that time, a number of randomized trials have addressed this topic, and cumulative results of these trials were published in a systematic review (Table 3).[11] The primary aim of the systematic review was comparison of 6-month response rates, either overall ($>30 \times 10^9$/L) or complete ($>100 \times 10^9$/L), between patients receiving short courses of dexamethasone and longer courses of prednisone. Four trials met criteria for assessment of the primary outcome (n = 459 patients). As illustrated in Table 3, there was variability in the corticosteroid protocol among trials, especially with regard to the number of dexamethasone cycles and the use of maintenance therapy. In addition, within individual reports, it can be difficult to ascertain details about the number of cycles required to achieve a response.

The pooled proportion of overall response (OR) or complete platelet count response (CR) at 6 months did not vary between dexamethasone and prednisone (OR = 54% vs 43%, relative risk [rr] = 1.16, 95% confidence interval [CI] 0.79-1.71, $P = .44$; CR = 37% vs 21%, rr = 1.49, 95% CI 0.50-4.48, $P = .48$). The only significant response difference was an increase in overall initial response by day 14 among patients receiving dexamethasone. When analyzed by cumulative corticosteroid dose (n = 3 trials), there was no effect of high cumulative dose (mean dose of 40 prednisone-equivalent units/kg, assuming 70-kg patient) on overall long-term platelet response (rr = 1.18, 95% CI 0.53-2.62, $P = .68$). Adverse event rates were 24 adverse events per 100 patients in the dexamethasone group compared with 46 adverse events per 100 patients in the prednisone group.

There is some difficulty in direct trial comparison and pooling of data due to the variability in treatment protocols outlined above.[11] Some trials allowed patient crossover or switching of therapy during the study period. Additionally, differences in response criteria and reporting of rescue therapies make data assimilation problematic. Even with published randomized trials, this remains a complex controversy.

Although there is a growing body of literature comparing different strategies of corticosteroid administration, with regard to long-term outcomes, there does not appear to be any conclusive evidence to favor one approach over the other. Decision-making may be informed by individual patient characteristics, such as consideration of side effect profiles, ability to adhere to longer courses of medications, and possible need for a more rapid response as demonstrated with dexamethasone.

Intensification of therapy

Rituximab

Rituximab, a monoclonal CD20 antibody, has been used as antineoplastic therapy for lymphoma at a standard dose of 375 mg/m^2 weekly for 4 weeks.[12] Recognition of peripheral B cell depletion led to exploration into rituximab as a therapy for autoimmune conditions. Rituxmab has also been shown to alter the T-helper type 1 cell (Th1)/Th2 profile and increase the number and function of circulating T regulatory cells.[13,14] Therapy with rituximab results in a platelet count response of $\geq 50 \times 10^9$/L in ~50% to 60% of patients, with 25% to 30% having a projected 5-year sustained response.[15] The only significant predictor of response in earlier studies was shorter disease duration.[16] Although these results may represent the higher likelihood of spontaneous remission early in the course of the disease, nonetheless they led to investigations of earlier administration of rituximab. Furthermore, combination therapy may provide enhanced immunomodulation, with higher levels of T-regulatory cells noted with combinations of low-dose corticosteroids and rituximab[17]; however, the duration of this change in profile and the effect on lasting remission remain unclear.

Two randomized trials have investigated dexamethasone alone or in combination with rituximab. Zaja et al[18] randomized treatment-naive patients to dexamethasone (n = 52) or dexamethasone plus rituximab (n = 49). They reported sustained response rates (platelet count $\geq 50 \times 10^9$/L after 6 months of treatment) of 63% vs 36%, suggesting that combination therapy was more effective at preventing chronic disease ($P = .004$, 95% CI 0.079-0.455). A fair number of patients in each arm (27% dexamethasone and 47% combination) required additional treatment with either corticosteroids or IVIg during the first 28 days of the study trial period. Safety monitoring was insufficient owing to early study closure secondary to meeting the efficacy end point; however, a trend toward increased grade 3 or 4 adverse events (10% vs 2%, $P = .082$, 95% CI −0.010 to 0.175) in the combination arm was detected. In a more recent randomized trial in 137 treatment-naive patients, similar sustained response rates (platelet count $\geq 50 \times 10^9$/L after 6 months of treatment) of 37% with monotherapy and 58% with combination therapy ($P = .02$) were observed, and the effect persisted with 12-month data (33% vs 53%, $P = .05$).[19] Furthermore, combination therapy significantly delayed time to first rescue therapy in responders ($P = .007$). The study also found an increase in the number of grade 3 or 4 adverse events in the combination arm ($P = .04$).

One additional pilot feasibility trial (n = 60) investigated the efficacy of rituximab in preventing treatment failures once standard therapy is discontinued.[20] The unique design of this randomized trial assessed both clinical and laboratory variables, using a composite outcome including platelet count $<50 \times 10^9$/L, significant bleeding events, and need for rescue therapy. At 6 months, there was no difference between standard of care alone and standard of care plus rituximab (65.6% vs 80.8%, rr = 0.81, 95% CI 0.59% to

Table 3. Randomized trials of high-dose dexamethasone vs prednisone

Study	Number of patients	Dexamethasone treatment group		Prednisone treatment group		6-Month response (dexamethasone vs prednisone)
		Dexamethasone regimen*	Prednisone equivalent†	Prednisone regimen*	Prednisone equivalent†	
Wei et al, 2016[43]	192	40 mg/day × 4 d for 1-2 cycles	14.2 mg/kg per cycle	1 mg/kg per day for 28 d	28 mg/kg	40.0% vs 41.2% ($P = 0.884$); platelet count >30 × 10^9/L with an absence of bleeding and no additional treatment
Bae et al, 2010[44]	151	40 mg/day × 4 d for 1-2 cycles	14.2 mg/kg per cycle	1 mg/kg per day for 28 d	28 mg/kg	33.3% vs 45.0% ($P = 0.33$); platelet count >30 × 10^9/L
Din et al, 2015[45]	94	40 mg/day × 4 d for 3 cycles with maintenance 0.035 mg/kg/day dexamethasone between cycles (n = 30) or without maintenance (n = 31)	42.8 mg/kg	1 mg/kg per day for 28 d	28 mg/kg	74.1% with maintenance ($P < .05$) vs 60% without maintenance vs 58.8%; platelet count ≥30 × 10^9/L and at least double baseline without bleeding
Mashhadi et al, 2012[46]	60	40 mg/day × 4 d for 1 cycle‡	14.2 mg/kg	1 mg/kg per day for 28 d	28 mg/kg	90% vs 53.3% ($P \leq 0.0001$); platelet count ≥30 × 10^9/L

Adapted from Mithoowani et al.[11]
*Dosing does not reflect therapy tapers, which were often not specified.
†Prednisone dose equivalent based on 0.75:5 equivalency ratio and estimated on a 70-kg patient.
‡Followed by a prednisone taper.

1.11%) with regard to the composite outcome. Longer-term data are clearly needed to fully understand this effect, given that results with rituximab monotherapy show a decline in response rates as far out as 5 years.

The typical dose of rituximab is extrapolated from use in malignant lymphoma, given normal T cell burden in patients with ITP; however, a lower fixed rituximab dose may be sufficient to provide immunosuppression and induce a platelet count response. A nonrandomized trial provided low-dose rituximab, 100 mg weekly for 4 weeks, upfront in treatment-naive patients.[21] Patients received 1 to 2 courses of 40 mg dexamethasone for 4 days alongside 4 weekly low doses of rituximab. Twenty-two patients (76%) had a platelet count ≥100 × 10^9/L at 6 months (median response duration 17 months, range 9-33). Unfortunately, interpretation of these data is limited by small numbers and lack of randomization. Further exploration of lower doses of rituximab for ITP is needed to determine whether this strategy would result in reducing side effects while achieving similar remission rates.

The addition of rituximab to corticosteroids is not currently standard of care. Before acceptance of this approach, additional consideration should be given to (1) impaired response to vaccines after rituximab therapy[22] and potential impact of compromised vaccination with subsequent splenectomy if needed, (2) the relative high cost of therapy and (3) the side effect profile of the additional rituximab and number of patients that would be exposed without potential benefit.[23]

Thrombopoietin-receptor agonists

Recognition of impaired platelet production in ITP expanded the development of thrombopoietin-receptor agonists (TPO-Ras), which act by stimulating platelet production, as novel therapies. There are currently two US Food and Drug Administration (FDA)-approved TPO-RAs, eltrombopag and romiplostim. These agents have both been extensively studied in adults and children with chronic ITP[24-33]; however, their use as therapy for newly diagnosed patients remains unclear. Although the primary mechanism of the TPO-RAs is not immunomodulatory, changes in the immune profile with increase in T regulatory cells have been shown after use.[34] Additionally, data suggest that a small proportion of patients experience a sustained increase in platelet count after use and even enter into remission.[35,36] Because these data are not from randomized trials, a causal relationship between remission and TPO-RA use can only be inferred. It is plausible that a combination approach of immunosuppression alongside increased platelet production may provide long-term benefit, similar to immunotolerance with high doses of factor administration for hemophilia patients with an inhibitor.

Limited data exist on using these agents in newly diagnosed patients, since they are not immunomodulating or curative. In a single-arm study, treatment-naive subjects received dexamethasone 40 mg for 4 days followed by eltrombopag 50 mg for 28 days.[37] The early complete response rate, defined as a platelet count ≥100 × 10^9/L at 33 days, was 83.3%, and the 6-month complete response rate was 50%. The likelihood of relapse-free survival, defined as maintaining a platelet count ≥100 × 10^9/L at 12 months, was 66.7%. Of the patients who did not responded to initial dexamethasone therapy, none responded to subsequent initiation of eltrombopag; therefore, it is likely not adequate as monotherapy.

These data provide preliminary safety and efficacy data on the addition of TPO-RAs as upfront therapy in combination with corticosteroids. Additional biological data are necessary to explore causality, and randomized trials could provide stronger evidence. In the absence of data, the cost of TPO-RA therapy in comparison with the relative inexpensive cost of corticosteroids is prohibitory in providing all newly diagnosed patients with this treatment, and its use should be reserved for patients refractory to standard first-line therapy.

A benefit of the TPO-RAs is that they do not convey additional immunosuppression risks, as occurs with other therapies such as rituximab. The most concerning side effects are thrombocytosis, thrombosis, transaminitis with eltrombopag, and bone marrow reticulin changes.[38-40] Eltrombopag was associated with cataract formation in early preclinical studies; however, in clinical trials the risk does not appear to be increased. It is unclear whether any additional risks would be increased with concomitant corticosteroid use or any new safety signals will be discovered.

Pediatric considerations

Providing treatment to an asymptomatic child with ITP likely does not favor exposing all children to therapy, given the already high rates of spontaneous remission in the absence of therapy. Nevertheless, modifiable disease factors that could reduce the likelihood of chronic disease in children have been sought. In a systematic review,[41] the only modifiable variable was administration of IVIg at diagnosis. The investigators have since completed a randomized prospective trial of IVIg compared with placebo for newly diagnosed children with ITP (n = 200). The preliminary results, presented in abstract form at the 2016 ASH annual meeting, indicated no difference in the rates of persistent disease at 6 months between the two groups (10.2% in the IVIg group and 10.4% in the observation group).[42] The study did show a lower incidence of grade 4 or 5 bleeding in IVIg group compared with placebo (8% vs 1%); however, given the low rates of bleeding, the number needed to treat does not justify exposure of all children to IVIg. There have been no additional randomized trials in pediatric ITP with a primary aim of preventing chronic disease.

Future directions

At present, there have been few well-designed randomized trials targeted at reducing chronic ITP in adults and children. Further prospective trials may be able to enhance our approach and improve overall outcomes. Adequate long-term follow-up will be necessary to determine whether relapse is truly averted or simply delayed. It will also be important to select novel composite outcomes that account for clinical events as well as evaluate cost and the added adverse events of combined therapies.

In addition to clinical trials, essential research should focus on identifying patients who would benefit from more intensive therapy: for example, the ability to determine those patients who will develop persistent or chronic ITP or identification of markers predictive of who would benefit most from a specific therapy. Additionally, understanding the link between treatment-induced biologic changes such as altered regulatory T cells and long-term remission rates may help predict those patients most likely to have a lasting response to therapy.

Limitations of existing trials, such as inclusion of long-term follow-up data, application of uniform response criteria, and randomization, should be addressed to allow for enhanced comparison of treatment strategies.

Recommendations from the 2011 ASH guidelines do not reflect recent randomized trials and combination strategies. In the setting of recent data, efforts are underway by ASH to appraise the quality of newer trials, consider the risk-benefit profile of these strategies, and provide updated guidelines.

For many adults diagnosed with ITP, the likelihood of long-term remission after corticosteroids remains low. For this reason, it is critical to ascertain whether there are available therapies that can prevent relapse. When used as single agents or in combination with standard corticosteroids, perhaps a balance between inducing remission and avoiding unwanted side effects can be achieved, and tailored therapies can be applied to patients most at risk for relapse.

Authorship

Contribution: C.E.N. conducted the literature review and wrote and edited the manuscript.

Conflict-of-interest disclosure: C.E.N. has consulted for Sanofi Genzyme. Off-label drug use: Rituximab and eltrombopag are discussed for newly diagnosed ITP.

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