Review Article

Pediatric immune thrombocytopenia (ITP) treatment

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Abstract: Pediatric immune thrombocytopenia (ITP) is a heterogeneous autoimmune condition with variability in etiology, bleeding phenotype, need for treatment and response to therapy, as well as duration of disease. Fortunately, many children have mild bleeding and experience spontaneous disease resolution, however it is not possible to predict which patients will have this outcome. For most children, initial management involves attention to screening for underlying secondary causes of ITP, followed by careful observation. When treatment is required, first line therapies are relatively standardized and aim to rapidly diminish bleeding risk. When ITP becomes persistent, chronic or otherwise necessitates alternative therapies, there is much less existing data on the optimal sequence of treatment choices and hence more variability in clinical practice. Further complicating management, there is no reliable way to predict which treatments will be effective, leading patients to be exposed to adverse effects of therapy without confidence in the degree of response. ITP management continues to evolve: as research expands our understanding of the molecular underpinnings of ITP, providers are increasingly able to refine and individualize treatment regimens. Further, novel therapeutics are being tested and used to treat adult ITP patients and these drugs may ultimately be applied to the benefit of children with this condition.

Keywords: Immune thrombocytopenia; pediatric immune thrombocytopenia; pediatric ITP; Evans syndrome; thrombopoietin agonists

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Introduction

Immune thrombocytopenia is the most common acquired bleeding disorder in the pediatric population with an approximate incidence of 5 per 10^5 children annually (1-3). Despite the overall high disease burden of ITP, many unanswered questions remain about its cause and how to best manage patients.

This review will focus on the initial management of pediatric ITP patients including early laboratory assessments, and front-line therapies. Significant gaps in knowledge have impeded stratifying the best second- and third-line treatment options for patients. Current experience with, mechanisms of action and clinical pearls for using individual drugs will be described. Finally, emerging therapeutics for novel genetic disorders associated with ITP as well as newer adult treatments which may eventually be applied to pediatrics are described.

Initial workup

Upon presentation with isolated thrombocytopenia, in addition to a complete history and exam, the following initial laboratory tests are obligatory: a complete blood count (CBC), reticulocyte count, review of peripheral blood smear. In addition, because they may help guide therapy

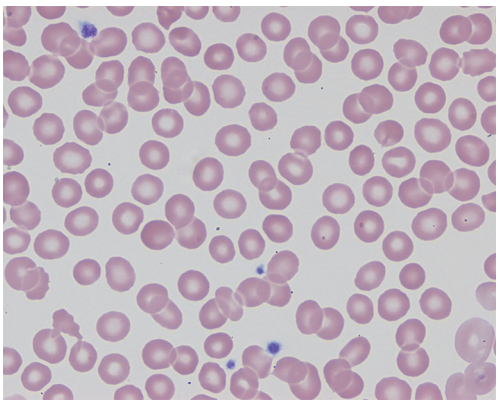

Figure 1 Peripheral smear in ITP. Peripheral smear in ITP shows a paucity of platelets with rare large and giant platelets. Normal white blood cell and red cell size and morphology is seen. H&E stain, 100×. Image courtesy of Dr. Amanda Grimes.

and uncover common underlying causes of ITP a direct antiglobulin test (DAT) and quantitative immunoglobulin levels are recommended (4). The peripheral smear should be normal with variable platelet size including large platelets and rare giant platelets (*Figure 1*). A DAT tests for the presence of autoantibodies against erythrocytes. The test is necessary if anti-D immune globulin (anti-D) therapy is being considered because active hemolysis is a contraindication to anti-D use, as will be discussed in detail below. In the absence of hemolysis, a positive DAT in a patient with ITP can provide evidence of more systemic immune dysregulation and warrants investigation of other underlying autoimmune conditions. An ITP patient with a positive DAT in association with hemolytic anemia has Evans syndrome, defined as two autoimmune cytopenias developing concurrently or in succession (5). Identification of Evans syndrome should prompt further evaluation for secondary causes of ITP and has implications for treatment. Some evidence suggests that a positive DAT, in the absence of hemolysis is associated with both evolution to chronic ITP and need for second line treatments (6). Immunoglobulin testing may uncover underlying immune defects which would significantly alter management such as common variable immune deficiency (CVID) or Selective IgA Deficiency. It is valuable to test quantitative immunoglobulins and a DAT prior to initiating therapy. IVIG may obscure low immunoglobulin levels and therefore delay detection of underlying immune deficiencies. Both IVIG and anti-D immune globulin will result in a positive DAT result because of passive antibody transfer.

Importance of defining ITP

A diagnosis of exclusion, primary ITP is characterized by isolated thrombocytopenia (platelet count $<100\times10^9$/L) without another identified disorder leading to immune thrombocytopenia (secondary ITP) (7). ITP can be classified both by the presence or lack of an underlying condition driving thrombocytopenia or by the duration of disease. Newly diagnosed ITP is defined as disease within three months of diagnosis and persistent ITP is disease with a duration between 3 and 12 months. Chronic ITP is defined as thrombocytopenia continuing beyond one year (7).

The ITP disease status and presence of secondary ITP are important factors driving treatment decisions. Causes of secondary ITP are discussed further under second line workup below. For those with longer duration of disease, second line therapies are more likely to be utilized, as quality of life deteriorates more the longer the disease is present (8,9). Refractory or long-standing disease should prompt evaluation for underlying infections, autoimmune or immunodeficiency/immune dysregulation disorders. Certain causes of secondary ITP have specific optimal treatments or contraindications to some therapies.

Treatment strategies

Cautious observation

The majority of children with newly diagnosed ITP are asymptomatic or develop only mild bleeding symptoms. More significant bleeding requiring treatment is more rare, and only 4% of pediatric patients having severe or life threatening bleeding with the incidence of ICH less than 1% (1,4,10). Unlike adult ITP patients, children have fewer comorbid conditions that compound bleeding risk (11). Children with ITP are much more likely than adults to experience spontaneous disease remission, with up to 70% of pediatric patients resolving by 6 months, compared to only 45% of adults (12). Given the lower risk of severe bleeding regardless of platelet count, the likelihood of spontaneous remission, and substantial side effects of ITP therapies, first line management for pediatric ITP is often careful observation. This is contrast to adult ITP patients for whom upfront treatment is considered when the platelet count is below 30×10^9/L even when asymptomatic or with minor mucocutaneous bleeding (3,4).

Caregivers should be educated on signs of bleeding and counseled on ways to minimize bleeding risk. Anti-platelet agents and anticoagulants must be avoided. Children need

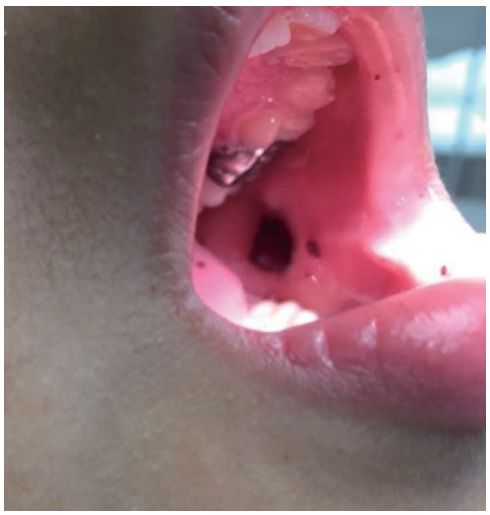

Figure 2 Mucosal purpura in pediatric ITP. The presence of mucosal bleeding, such as oral purpura (shown in image), menorrhagia, hematuria, hematochezia or melena are indications for treatment in pediatric ITP.

to abstain from contact and collision sports and other high-risk activities such as trampoline use. Treatment is indicated if parents do not feel they can appropriately limit their child's activity, such as in the case of an active toddler or adolescent engaging in sports. Hematology follow up is essential to ensure compliance with activity precautions, monitor for bleeding symptoms, and ensure no other concerning signs or symptoms suggest the need to evaluate for an alternative diagnosis. Psychosocial issues such as compliance concerns or inability to bring the child readily to medical care must be accounted for when deciding to observe. If appropriate return to medical care cannot be guaranteed, the patient should be treated.

Children with severe or emergent bleeding such as hematuria, hematochezia, or other internal hemorrhage such as intracranial bleeding require immediate and often multi-modal treatment. Those with mucosal bleeding (such as wet purpura, epistaxis, and menorrhagia) (Figure 2) have increased risk for severe bleeding and in this scenario, treatment is indicated to rapidly achieve a hemostatic platelet count.

Ultimately, the decision to treat pediatric ITP patients is an individualized one and shared decision making between the patient, caregiver and physician is critical.

For children requiring therapy but without life threatening bleeding, corticosteroids are the recommended first line therapy over IVIG or anti-D (3). Corticosteroids are suggested over IVIG or anti-D by the 2019 American Society of Hematology ITP guidelines, due to low cost, universal availability, ease of outpatient administration, no exposure to multiple blood donors and overall minimal side effects associated with short courses of steroids (3). Importantly, severe life threatening side effects are reported for IVIG and anti-D. As described below, anti-D has a black box warning for intravascular hemolysis (13) and IVIG carries a black box warning for both renal failure and thrombosis (14,15). Studies on the effectiveness of steroids and formal trials comparing first line agents are lacking (3). Because oral steroids have a slower time to effect, IV steroids, IVIG or anti-D are more appropriate when a rapid rise in platelets is needed in the setting of severe mucosal bleeding. Description of the three front line medications for ITP is found in *Table 1*.

Corticosteroids

Several corticosteroid regimens are utilized in practice, but have not been directly compared. Guidelines from the American Society of Hematology recommend a 5–7 day course of prednisone dosed at 2–4 mg/kg/day (3). Seventy-five percent of children respond to steroids, with platelets recovering to hemostatic range by 2–7 days (16) (*Table 1*). If a more rapid rise in platelets is desired, IV methylprednisolone may be used. Studies comparing outcomes between anti-D versus methylprednisolone (17) and comparing methylprednisolone with dexamethasone (18) showed similar response rates with minor side effects in all groups.

Mechanism

There are multiple molecular mechanisms of action for corticosteroids in ITP. Steroids may increase platelet production (19), decrease autoantibody production (20), decrease platelet clearance (21), and reduce structural changes at the endothelium thereby decreasing bleeding and platelet consumption (22).

Risks and adverse events

There are substantial side effects of corticosteroid therapies, especially if used for a prolonged duration at moderate to high doses. Common side effects include weight gain, mood changes, sleep disturbance, gastritis, GI bleeding, hypertension, hyperglycemia, and when used chronically, cataracts and osteoporosis. As an immune suppressive

Table 1 Comparison of first line therapies for pediatric ITP

Medication	Dose	Duration	Time to response	Response rate	Cost*	Common side effects
Prednisone	2–4 mg/kg/day Max 120 mg daily	5–7 days, no taper	2–7 days	50–77%	$786.00	Gastritis, mood changes, weight gain, hypertension, hyperglycemia
IVIG	1 g/kg ×1 2nd dose may be given if needed	Single dose	24–48 hours	>80%	$2,492	Headache, nausea, aseptic meningitis
Anti-D immune globulin	50–75 µg/kg ×1	Single dose	24–48 hours	~75%	$2,035	Headache, chills, fever, hemolysis

*estimated for 20 kg child.

medication, steroids should not be used in the setting of severe infection and can specifically result in re-activation of varicella. Given the substantial adverse effects of corticosteroids, they should be limited to as brief a course as possible, especially in children. If no response is seen, alternative therapies should be pursued (3).

Intravenous immune globulin

Intravenous immune globulin (IVIG) is a commonly used agent for upfront treatment of pediatric ITP. The use of this therapy in children is specifically discussed in detail elsewhere in this issue.

Anti-D immune globulin (Rho(D) immune globulin, anti-D)

Anti-D is another frontline option in children who require treatment. Anti-D has advantages as a rapid IV infusion with lower donor exposure than IVIG. Anti-D typically induces a rise in platelet counts within 24–48 hours for approximately 50–77% of children (4,23).

Mechanism

While the mechanism is not fully understood, it is postulated that anti-D antibodies coat circulating erythrocytes, which then travel to the spleen. Opsonized red cells saturate Fc receptors on reticuloendothelial cells. This allows antibody coated platelets to evade binding by the spleen thereby increasing their survival in circulation (24). Because anti-D requires binding to Rh-antigens on erythrocytes, it is only effective for individuals who are Rh positive. Additionally, anti-D is generally ineffective in asplenic patients.

Risks and adverse events

The use of anti-D has decreased since it was first approved for use in ITP in 1995. A major contributor to the decreased utilization of anti-D was the FDA black box warning focused on severe intravascular hemolysis issued in 2010 (13). Though rare, anti-D's most feared side effect is intravascular hemolysis leading to severe anemia, multi-organ failure, acute respiratory distress syndrome and death (13). Although these life threatening events occurred in predisposed patients (25), the FDA further advises close monitoring for 8 hours post-infusion with periodic urine assessment looking for evidence of hemolysis. Supportive care is recommended for individuals who experience severe intravascular hemolysis which may include transfusions or respiratory support. Because anti-D binds erythrocytes and targets them for destruction by the reticuloendothelial system, some degree of hemolysis is inherent with anti-D use. The average decrease in hemoglobin following anti-D use is 1.7 g/dL (23). Other side effects are less severe and include fevers, chills and headache occurring in 1–2% of patients (26).

Due to the expected hemolysis, children should be screened for pre-existing hemolysis or risk factors prior to receiving anti-D. A DAT is a recommended component of the initial laboratory evaluation of ITP patients both to determine safety and may also have clinical implications (4,6). Administration should be avoided in children with abnormal renal function and due to risk of inducing a severe reaction, anti-D should not be given in known or suspected EBV infection, or highly febrile children (27).

Emergency care

Regardless of disease status (new, persistent, or chronic), for severe uncontrolled bleeding, multiple treatment modalities may be applied together including platelet transfusion, IV steroids, IVIG and/or anti-D. If bleeding does not improve rapidly and the patient continues to have major bleeding, emergency splenectomy may be the only option.

While platelet transfusion is usually avoided because transfused platelets are thought to be rapidly consumed in the setting of ITP, some patients may have a modest increase in platelets and have reduction in bleeding (28,29). Individuals who have a response to platelet transfusions may represent a distinct ITP phenotype that is T-cell mediated as opposed to antibody-driven (30). Front-line therapies given in concert with transfusions may prolong the life-span of transfused platelets (16,29).

Increasingly, thrombopoietin receptor agonists (TPO-RAs) are being used earlier in the management of pediatric ITP. TPO-RAs may have a role as adjunct in the setting of severe or life-threatening bleeding. While these agents do not generate a rapid platelet count increase, they may help sustain platelet counts after the effect of initial IV therapies wane. In the case of ICH, medical management is initiated immediately and emergency splenectomy and/or neurosurgical intervention considered.

Secondary ITP diagnostic workup

Children with chronic ITP warrant further evaluation for secondary ITP, or underlying conditions that lead to immune thrombocytopenia. Similar to those with long standing single cytopenias, children with multi-lineage autoimmune cytopenias require more extensive testing. Evans syndrome, defined as two or more cytopenias, either occurring concurrently or sequentially (31), is most often characterized by ITP and autoimmune hemolytic anemia (AIHA) (32). Evans syndrome was previously defined as idiopathic, but increasingly underlying causative lesions are being identified, including novel genetic syndromes (33).

Conditions associated with secondary ITP include lymphoproliferative disorders [e.g., autoimmune lymphoproliferative syndrome (ALPS)], immunodeficiency syndromes (e.g., CVID, DiGeorge syndrome, SCID), rheumatologic conditions (e.g., Systemic lupus erythematosus (SLE), Antiphospholipid antibody syndrome, Sjögren syndrome, juvenile rheumatoid arthritis), malignancies (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma), or chronic infections (e.g., HIV, hepatitis, cytomegalovirus, *H. Pylori*). In the setting of chronic infections, priority should be given to treating the underlying condition, which in itself, may ameliorate thrombocytopenia (34). For example, HIV should be managed with antiretrovirals, and if ITP requires treatment, IVIG, steroids or anti-D can be used. In the setting of Hepatitis C virus infection, treatment involves antivirals and interferon. Interferon may drop platelet counts, and IVIG is preferentially used to treat thrombocytopenia in this setting, as steroids may increase viral loads (34).

Work-up is tailored based on the child's history, individual risk factors, physical exam findings, and family history. Minimum screening for disorders frequently implicated as causing secondary ITP or those for which diagnosis alters management substantially are outlined in *Table 2*. While a bone marrow evaluation is not recommended for new pediatric ITP patients and is not required prior to starting therapy, in the setting of chronic, refractory disease, it may be considered (3).

Second line therapy options

Second line agents are indicated for children who do not respond or relapse after first line agents. These first line therapies are utilized with the goal of rapidly increasing the platelet count, thereby mitigating severe bleeding risk, but are not intended for use as a maintenance therapy, or to elicit a durable response in those with persistent or chronic ITP. Second line therapies in children are similar to those used in adults, however splenectomy is avoided in children given the likelihood of spontaneous resolution in pediatric populations and potential for complications. Splenectomy is generally only considered after failure of medical management including combination therapy in a child over age 5 with ITP for at least 12 months, or in the setting of uncontrolled life-threatening bleeding.

TPO-RAs: eltrombopag and romiplostim

Increasingly TPO-RAs are being utilized as the initial second line agent for pediatric ITP patients who do not respond to upfront therapies (corticosteroids, IVIG or anti-D). The most recent American Society of Hematology guidelines, published in 2019, suggest the use of TPO-RAs over rituximab and splenectomy in children (3). In contrast, selection of TPO-RAs versus rituximab or splenectomy in adults depends more heavily on patient preferences

Table 2 Recommended testing for multilineage cytopenias or chronic ITP

Test	Disease evaluated
DAT	SLE, Evans syndrome, other autoimmune disorders
ANA	SLE, other rheumatologic disorders
Antiphospholipid antibodies	APS, SLE
Quantitative immunoglobulin	CVID, XLA, specific antibody deficiency, selective IgA deficiency, IgG subclass deficiency, SCID
Flow cytometry for double negative T cells (ideally 4 color flow) TCRα/β+ CD3+ CD4-CD8-	ALPS

ALPS, autoimmune lymphoproliferative syndrome; ANA, antinuclear antibody; SLE, systemic lupus erythematosus; CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinemia; APS, antiphospholipid antibody syndrome; SCID, severe combined immunodeficiency.

regarding use of daily medications and feelings about surgical interventions (3).

Eltrombopag was approved for use in children with chronic ITP in 2015 following two multicenter, double-blind, placebo controlled trials (PETIT and PETIT2) demonstrated its efficacy at raising the platelet count with a favorable side effect profile (35,36). Romiplostim was approved in December 2018 for use in children over 1 year of age who had refractory disease persisting beyond 6 months, however it had been used off-label for many years prior to this (37). The majority of children who received eltrombopag or romiplostim in clinical trials had a favorable response to the drugs (35,36,38-40).

Selecting eltrombopag or romiplostim depends on the preferences of the patient, their family and comfort of the provider with prescribing one or the other. Differences in administration heavily impact choice of TPO-RAs. Eltrombopag is dosed once daily and is available as an oral tablet or as a powder for suspension (41). A more challenging issue with eltrombopag administration in the pediatric population is the need to space doses 2 hours before or 4 hours after dairy consumption, as divalent cations such as calcium decrease its absorption (42). Romiplostim is dosed as a weekly subcutaneous injection. Romiplostim is not FDA approved for home administration, so families may be required to make weekly clinic visits to receive treatment. If patients are transitioned between one TPO-RA to the other, the likelihood of a response with an alternate agent is approximately 75% (43).

Mechanism

Both eltrombopag and romiplostim act by binding the TPO receptor, *c-mpl*, thereby driving increased platelet production by megakaryocytes. Structurally homologous to endogenous TPO, first generation TPO-RAs, formulated as pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) and recombinant human thrombopoietin (rhTPO), induced antibody development against endogenous TPO (44-46). However, second generation TPO-RAs lack sequence homology with endogenous TPO, bind different regions of the TPO receptor, and are less immunogenic (47). Aside from stimulating platelet production, there is also some evidence to suggest that TPO-RAs have immunomodulatory effects (48,49). This is being studies currently in pediatric ITP populations (NCT03939637).

Romiplostim is comprised of two peptides conjugated to the IgG1 heavy chain and binds the extracellular binding domain of *c-mpl*. Eltrombopag, is a small, non-peptide molecule which interacts with the juxtamembrane domain of the TPO receptor (*Figure 3*). Both romiplostim and eltrombopag stimulate platelet production via multiple signaling pathways including the SHC-Ras-Raf pathway, JAK-STAT pathway and PI3k-Akt signaling (50).

Risks and adverse effects

Overall, the TPO-RAs are well tolerated by pediatric patients and shown to be safe in clinical trials.

Thromboembolic events are a concern in ITP patients treated with TPO-RAs, but recent data show the risk does not appear to be elevated compared to children with ITP who were treated with other therapies (50). Concern for thrombosis also draws largely on experience in adults, who have other comorbidities contributing to thrombosis risk (50). Pediatric patients have not developed thrombi while on TPO-RAs in clinical trials, but theoretically,

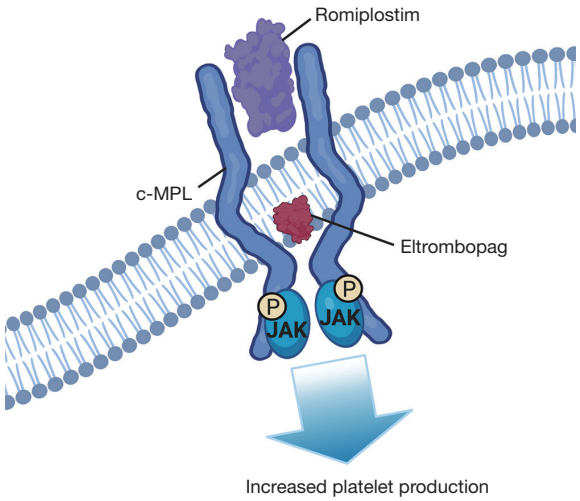

Figure 3 Binding regions of romiplostim and eltrombopag. Both romiplostim and eltrombopag bind and stimulate the thrombopoetin receptor, *c-mpl*. Romiplostim binds at the distal cytokine homology 2 (CRH-2) domain while eltrombopag binds a transmembrane region. Image created with BioRender.com.

adolescents with additional risk factors such as obesity or estrogen contraceptive use may have a risk more similar to adult ITP patients (38,51).

Based on lens changes in animal models, cataract development was an initial concern with TPO-RA use. In the PETIT2 trial, 1 patient had progression of an existing cataract and another developed a new cataract, however both patients were also treated with steroids (36).

By stimulating megakaryocytes, which then release cytokines that promote collagen synthesis by marrow fibroblasts, both eltrombopag and romiplostim can lead to reticulin fiber deposition in the bone marrow (52,53). However, in studies of both agents, bone marrow fibrosis was extremely rare, and when it did develop, was mild and did not impact peripheral blood counts. Fibrosis also appears to be reversible on discontinuation (54,55).

Eltrombopag has hepatic metabolism and drug levels may be up to 41% higher in the setting of even mild hepatic dysfunction (56). Eltrombopag can cause transaminitis, however this is typically mild (36,39). Finally, as a chelator, eltrombopag can also result in decreased iron absorption and lead to iron deficiency (35,57).

Because divalent cations, such as calcium, decrease eltrombopag absorption, it must be taken on an empty stomach and doses should be timed at least 4 hours before or after dairy and other calcium rich food consumption (42). This factor significantly limits the use of eltrombopag in children.

Rituximab

Though not FDA approved for use in ITP, based on experience with other autoimmune conditions, rituximab has long been used for patients with ITP and inadequate response to upfront therapy. Dosing in ITP is typically 375 mg/m^2 in 4 weekly infusions (58). While TPO-RAs have around 70–80% response rate (35,36,59), reported response rates to rituximab are approximately 60% (60). Response to rituximab is frequently not sustained, with reports showing only 26% of children maintain their platelet counts at 5 years from rituximab dosing (60).

Ascertaining the underlying cause of secondary ITP is critical when planning to use rituximab for refractory disease. In those with SLE, rituximab may have better response rates than primary ITP patients (61). However, there are conditions where rituximab should be avoided. In ALPS, those who receive rituximab are at increased risk of having prolonged B cells depletion and hypogammaglobulinemia. Prolonged neutropenia is reported in ALPS patients and those with underling immunodeficiencies treated with rituximab (33,62). In general, we recommend all children receiving rituximab have immunoglobulin levels tested and be screened for normal B cell populations as a baseline prior to dosing. Some patients who receive rituximab experience symptomatic hypogammaglobulinemia and increased infection risk (63). Patients with underlying immune defects such as CVID are at particular risk for this outcome (63).

Mechanism

Rituximab is a chimeric monoclonal antibody directed against CD20, expressed on B cells (64). Once bound, rituximab triggers B cell destruction via complement or Fc-receptor mediated clearance (65). With depleted B cells, the production of auto-antibodies directed against platelet glycoproteins is reduced.

Risks and adverse effects

The most common adverse events associated with rituximab are related to infusion reactions including fevers, myalgias, hives, chest tightness, headache and hypertension. Severe side effects are exceedingly rare in children with ITP and include serum sickness or progressive multifocal leukoencephalopathy (66). Finally, rituximab can reactivate

hepatitis B infection resulting in fulminant, even fatal disease (66).

Splenectomy

In the past, splenectomy was a commonly utilized second line treatment, but is now rarely performed (67,68). When used, it should be reserved for children with significant bleeding, over the age of 5, who have tried and failed available medical management, including combination therapies. Unless being used for emergency bleeding control, an invasive and permanent intervention such as splenectomy should also be limited to those with chronic ITP due to the high likelihood of spontaneous disease resolution (3). Prior to surgery, vaccinations should be up to date including *Haemophilus influenza* type B, meningococcal and pneumococcal 13-valent conjugate vaccines, followed by pneumococcal 23-valent vaccine (3).

Pediatric response rates to splenectomy are around 60-70% within a day of surgery, hence its application in the case of life-threatening bleeding. Over 4 years, 80% of splenectomized children maintain a response (16).

Risks and adverse effects

Splenectomy results in an increased risk for infection, both in the immediate post-operative period as well as an overall life-long increased risk for sepsis or invasive infection. There is increased risk for deep venous thrombus and pulmonary hypertension development as well, though most reports on these outcomes focus on adults. In addition, there is mortality and morbidity risk associated with the surgery itself (69).

Alternative treatments

After first- and second-line therapies have been tried, the next therapy option is selected in discussions between the medical team, caregivers and patient. In a study focused on treatment choices from the ITP Consortium of North America, the most common reason to select a particular agent was the possibility of long-term remission, followed by parental or patient preference, and side effect profile (68). Other factors which impact decision making include the provider's experience and ease of administration for the individual drugs (33).

There is a paucity of large, formal studies evaluating outcomes of third line agents in pediatric ITP and certainly, there are no randomized controlled trials comparing the many available therapies directly. Other agents used as third line management include purine analogues (azathioprine, mercaptopurine), mycophenolate mofetil, sirolimus, cyclophosphamide, cyclosporine A, dapsone, danazol and vincristine. Collectively, initial response rates for these drugs range from around 30–60% (3).

For refractory patients, combination therapies may also be trialed. In our experience, using medications which target different disease mechanisms is more efficacious.

Emerging therapies

Targeted therapies

The genetic and molecular understanding of ITP pathogenesis is expanding. Increasingly, patients thought to have primary ITP without a typical response to therapies or an unexpected disease course, are found to carry novel genetic alterations resulting in loss of immune tolerance. Armed with this knowledge and increasing availability of genetic testing, an individual patient's treatment regimen can be refined to their specific condition, rather than trialing a series of broad immune suppressive agents.

CTLA-4 haploinsufficiency and LRBA deficiency

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is constitutively expressed on regulatory T cells and inhibits T cell activation (70,71). LPS-responsive beige-like receptor anchor protein (LRBA) is thought to be a regulator of CTLA-4 function. Impacting the same molecular signaling pathway, both CTLA-4 haploinsufficiency and LRBA deficiency lead to abnormal activation and proliferation of T cells resulting in loss of immune tolerance (72-75). While patients have other features including recurrent infections, hypogammaglobulinemia, and lymphocytic infiltration of multiple organ systems, ITP is a feature of both conditions (70,76,77). Abatacept, a fusion protein comprised of the extracellular domain of CTLA-4 bound to IgG_1, restores CTLA-4 and ameliorates symptoms of autoimmunity (76,78).

Both these conditions present in the early adolescent population and are an important consideration for chronic ITP patients with additional features of immune dysregulation (74).

PI3Kδ syndrome

Gain-of-function mutations in PI3Kδ lead to activation of the mTOR pathway and, though Akt phosphorylation,

may promote effector T cell development (79). Presenting in children age 1 to 7 years of age, those with PI3Kδ syndrome have autoimmune cytopenias, lymphadenopathy, hepatosplenomegaly and immunodeficiency (80). Sirolimus is an mTOR inhibitor and has been used in treatment of PI3Kδ syndrome. A selective PI3Kδ inhibitor, Leniolisib is currently in clinical trials (81).

STAT1 and 3 gain-of-function

Excess STAT1 signaling results in skewed Th17 differentiation and hyperresponsiveness to IFN-γ (33). Clinically, patients experience autoimmunity and chronic mucocutaneous candidiasis (82). When stimulated, Janus kinase (JAK) recruit STATs, leading to signal transduction. Ruxolitinib, a JAK inhibitor, acts to correct the molecular defect in these patients, though STAT levels may not correlate directly to symptomatology (83). Excess STAT3 activation leads to suppressed apoptosis via cytokine signaling, including IL-6 (84). Tocilizumab, an IL-6 inhibitor and ABT-737, which targets anti-apoptotic protein Bcl2, are being used as treatments for this condition (85).

Potential future pediatric therapies

A number of newer agents are being employed for adult ITP management which may eventually have utility in pediatric populations.

A transcytosis receptor, the neonatal Fc receptor (FcRn) regulates circulating IgG (86). Inhibition of the FcRn, results in increased lysosomal IgG degradation and subsequently decreases serum IgG levels. Efgardigomod and rozanolixizumab are both novel FcRn receptor antagonists. Phase 2 trials of efgardigomod, a weekly intravenous infusion, showed efficacy and favorable side effect profiles in adults with refractory ITP (87). Rozanolixizumab, a subcutaneous injection, raised platelet counts and decreased IgG levels with minimal side effects in phase 2 trials of adult ITP patients with multiply refractory disease (88). It is currently in phase 3 trials for adult ITP patients (NCT04200456). Neither FcRn antagonist has been studied in children.

Avatrombopag is an oral TPO-RA first approved in adults with ITP and chronic liver disease. As of June 2019, its approval was expanded to use in adults with chronic ITP who failed prior therapies (89). Avatrombopag is attractive as a potential future option in children because it is oral and does not have the same dietary restrictions that accompany eltrombopag (90). At the time this article was being written, avatrombopag was going into pediatric clinical trials (NCT04516967).

Fostamatinib is a spleen tyrosine kinase (SYK) inhibitor which inhibits Fc receptor mediated platelet destruction. It was approved in 2018 for use in refractory adult ITP patients. A phase III study in multiply refractory adult chronic ITP patients demonstrated 43% of patients achieved a platelet count of ≥50,000/μL at 3 months (91). Due to concerns on effects on cartilage in growing children, it has yet to be studied in pediatrics.

Conclusion

For many children ITP symptoms are mild and self-resolve, and it would initially seem that treatment is straight forward. However, pediatric ITP is a heterogeneous disorder, with each patient's case differing in bleeding phenotype, duration of disease and response to therapy. In particular, for those with chronic ITP, multi-lineage cytopenias or individuals with thrombocytopenia which is a component of another underlying systemic disorder, management is even more complex. The field of ITP study continues to identify more genetic risk factors. These can now be leveraged to both elucidate the cause of an individual child's ITP, and be used to develop better targeted therapies in the future.

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