REVIEW ARTICLE

Diagnosis of immune thrombocytopenia, including secondary forms, and selection of second-line treatment

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Abstract

This article summarizes our approach to the diagnosis of immune thrombocytopenia (ITP), its secondary forms, and choice of second-line treatment options. We very briefly summarize first-line treatment and then utilize a case-based approach. We first explore persistent, chronic ITP in a younger female. We consider many possibilities beyond primary ITP e.g., hypogammaglobulinemia, chronic infection, and anemia, and how to approach their diagnosis and management. The journey continues throughout pregnancy and the post-partum period and eventually includes fourth-line treatment after a late relapse. We then consider an older male, emphasizing differences in diagnostic considerations and management. The focus is on initiation and continuation of second-line treatment, the pros and cons of each option, and briefly the impact of treatment choices related to the endemic presence of severe acute respiratory syndrome coronavirus 2. During the review of potential second-line treatment options, we also briefly touch upon novel treatments. Finally, there is a short section on refractory disease drawn from our previous extensive review published in February 2020.[1] The clinical nature of the discussions, replete with figures and tables and with the interspersion of pearls regarding efficacy and toxicity at different ages and genders, will serve the reader in the management of "typical" adult patients who develop persistent and chronic ITP.

Introduction

Immune thrombocytopenia (ITP) is a complicated disease because of its heterogeneity and lack of diagnostic markers making selection of treatment difficult. Perhaps the most straightforward part of management is at presentation of ITP. If the platelet count is very low and no other findings are present, the worldwide consensus treatment is steroids. Whether dexamethasone, prednisone/prednisolone (prednis[ol]one), or intravenous (IV) methylprednisolone is used, the response rate and side effects are relatively predictable. IV methylprednisolone or dexamethasone increases the platelet counts faster and may have fewer side effects than have weeks of prednis(ol)one treatment.[2] Questions revolve around whether to add IV immunoglobulin (IVIG), and/or platelet transfusion. While the latter is rarely appropriate if there is serious bleeding and/or the diagnosis is unclear, an analysis based on medical records in the USA identified that as many as 25% of ITP patients receive platelet transfusion,[3] which is far too many.

The management of ITP becomes more complicated if other findings arise, if patients do not respond to steroids, or if patients continue to require treatment. Both the American Society of Hematology guidelines and an international consensus report emphasize that continued steroid use beyond 6 weeks is to be avoided.[4,5] Compliance with this strong recommendation entails earlier use of "second-line" therapy in patients with ITP, a practice already gaining traction. However, the definition of "early" remains fluid; "early" can be at 1 month of steroid treatment to allow discontinuation of steroids. "Early" can also be in the first 3 months when ITP is "newly diagnosed.[6] These ill-defined distinctions are one reason for substantial variation in the management of ITP. Another is the uncertainty of diagnosis. A third, the focus of this discussion, is how to select second-line treatment.

This review focuses on the initiation of second-line treatment reviewing the pros and cons of different agents utilizing a case-based approach by first exploring ITP in a young female and continuing throughout her pregnancy. The review then outlines diagnostic considerations and management in an older male with particular attention to secondary ITP in both patients.

Section I. A young female patient with immune thrombocytopenia: second-line treatment options

The patient's history

A 20-year-old female returns home from college. She notes heavier periods and easy bruising. Her internist sees that she is pale and has visible petechiae on her arms. Complete blood counts show mild anemia (hemoglobin 10.2 g/dL) and thrombocytopenia with a platelet count of $5x10^9$/L The internist sends her urgently to the emergency room concerned that she might possibly have leukemia. There is no hepatosplenomegaly or lymphadenopathy or other abnormal findings on physical examination.

Review of a peripheral blood smear reveals no blasts or abnormalities of other cell lines although her mean corpuscular volume is low (72 fL) and several of her very few platelets are large. She is diagnosed with ITP and given prednisone 1 mg/kg. Over the next few days, she has typical steroid-related side effects: feeling "a little crazy", insomnia and abdominal pain. Her bruises and petechiae disappear, and her period ends. Her hematologist prescribes oral iron supplements and changes her prednisone to dexamethasone 40 mg daily for 4 days. Her steroid-related side effects worsen during the 4 days on dexamethasone 40 mg; however, she soon feels better with no further petechiae, bruising, or menstrual bleeding noted.

Her platelet count normalizes to $147x10^9$/L and her hemoglobin improves to 11.2 g/dL. She begins checking her blood counts monthly. The improved complete blood count with a nearly normal mean corpuscular volume excludes bone marrow failure, and also thalassemia trait or microangiopathic hemolytic anemia. Similarly, the normal hemoglobin and neutrophil count do not suggest Evans syndrome. Her platelet counts remain in the normal range and her hemoglobin improves to the normal range. At her next visit, her platelet count has decreased to $80x10^9$/L. One month later, her platelet count is $28x10^9$/L with continued normal hemoglobin and infrequent small bruises. With her platelets trending downward, second-line treatment for her ITP is considered.

There is less urgency to consider secondary ITP or a missed diagnosis since she is doing well but at any change of management, it is good practice to re-evaluate. Below we consider some of the "*what if*" clinical scenarios for this young female.

What if the patient is persistently anemic despite iron supplementation?

If the mean corpuscular volume is low, consider workup for underlying thalassemia trait or iron deficiency with the latter being common in the setting of heavy menses. Iron replacement is not always straightforward; using oral replacement every other day may be equally effective as daily administration.[7] Resorting to IV iron may be important especially if oral replacement does not correct iron status and/or there are signs of a chronic inflammatory disease. If the mean corpuscular volume is high, bone marrow failure must be considered. There could also be pernicious anemia secondary to vitamin B12 deficiency or an autoimmune hemolytic anemia, such as Evans syndrome. Another possibility is microangiopathic anemia with thrombocytopenia, whether in the form of thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. In these cases, there would likely be increased reticulocytosis. While individually each of these conditions is rare, having one of many rare conditions would not be as surprising.

If heavy menstrual bleeding persists, a progesterone-based approach is superior to an estrogen-based approach in women with ITP as the former raises the platelet count.[8] While estrogen-based therapies are more commonly used in general practice for heavy menstrual bleeding, they might worsen ITP.[9] In contrast, progestational agents have previously been tried as treatment in ITP with good effect. Progesterone may be administered orally at a dose of 5-10 mg daily or medroxyprogresterone acetate (Depo-Provera) can be given intramuscularly once every 3 months but the latter may result in intermittent vaginal bleeding.

What if the immune thrombocytopenia is part of a larger spectrum of autoimmune disease?

Our patient's immunoglobulins were normal, so she does not have common variable immunodeficiency (CVID) or IgA deficiency. Neither the diagnosis of CVID nor that of IgA deficiency requires a history of infections; in fact, there may be a history of autoimmunity, especially in a patient presenting with ITP, or allergy. Furthermore, the diagnosis of CVID is often not made until after the age of 30.[10] The IgG level does not have to be very low in cases of CVID presenting as ITP, which may account for the lack of infectious history in many of these patients. In cases of CVID, and possibly systemic lupus erythematosus with ITP, there may have been an episode of ITP years before treated with steroids, with the patient having gone into remission for years without any medication (Charlotte Cunningham-Rundles, *personal communication*). Other immunodeficiency states are also associated with ITP, not all of which will include hypogammaglobulinemia.[11]

Given our patient's age and gender, it would not be surprising if she was positive for antinuclear antibodies and was developing systemic lupus erythematosus. A study from France suggests that hydroxychloroquine may be considered in an ITP patient positive for antinuclear antibodies.[12] Nor would it be surprising if her thyroid tests were abnormal, as thyroid disorders in young women with ITP are usually autoimmune.[13-16] In a young woman, there is a relatively high rate (as high as 5-10%) of abnormalities

of thyroid function and this finding may be more frequent in women with ITP. The question remains of whether these conditions should be tested for in all patients or only if there are suggestive findings. If the patient is fatigued that would necessarily instigate an evaluation of underlying causes that would include hypothyroidism. Fatigue and depression are relatively common but poorly understood in ITP,[17] thus requiring comprehensive evaluation.

What if the immune thrombocytopenia is secondary to a subclinical viral infection?

Multiple viruses have been associated with ITP. In children, ITP is often thought to be a post-infectious sequela. There may also be an underlying viral disease which is asymptomatic and thus eludes detection. It remains unclear whether all patients with ITP should be screened for hepatitis C and human immunodeficiency virus; with the coronavirus pandemic, it might be appropriate to screen for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[18] Treatment of these three viral infections would alter ITP management. The primary treatment for both hepatitis C and human immunodeficiency virus would likely increase the platelet count. However, if hepatitis C has progressed to cirrhosis, the platelet effects of antiviral treatment may be limited. Another viral infection that could be subclinical is cytomegalovirus which might be revealed only by atypical lymphocytes and/or mildly elevated liver tests. Cytomegalovirus can worsen ITP in patients receiving immunosuppressive treatments because these agents will activate the cytomegalovirus and thus worsen the ITP making it more resistant to treatment.[19,20] *Helicobacter pylori* may "cause" ITP, but only in certain places, e.g., Japan and Italy, is searching for it at diagnosis of ITP routine and is its eradication a uniformly effective approach to ITP.[21]

What if the patient has an inherited thrombocytopenia?

Our patient's bleeding resolved in parallel with the improvement of her platelet count, which suggests that she does not have platelet dysfunction, as seen in Bernard-Soulier or Wiskott-Aldrich syndrome. Furthermore, she does not have any syndromic features consistent with an inherited thrombocytopenia. Review of her prior records revealed that she has had at least one prior normal platelet count.

The stability of her blood counts after initial treatment excludes cyclic thrombocytopenia which is an often-forgotten form of inherited thrombocytopenia.[22] There are very many forms of inherited thrombocytopenia and new ones seem to be discovered regularly. Certain features should suggest an inherited thrombocytopenia:[23,24] (i) other family members with thrombocytopenia; (ii) no past normal platelet count; (iii) too many too large platelets on a blood smear (not all inherited thrombocytopenias have macrothrombocytes but most do); (iv) features of a syndrome such as thrombocytopenia-absent radius syndrome; (v) failure to respond to treatment for ITP, such as IVIG and steroids: (vi) bleeding out of proportion to the platelet count e.g., Bernard-Soulier syndrome, Wiskott-Aldrich syndrome, RUNX-1 mutations; and (vii) a relatively stable platelet count. In the absence of an apparent specific syndrome, whole exome screening may be helpful, although this approach is effective in less than half of such cases.[25] Ideally this possibility would be explored in conjunction with an experienced geneticist. The importance of making a precise diagnosis is not limited to the management of the platelet count *per se*, but extends to the associated medical problems including a possible propensity to autoimmune conditions, malignancy, or bone marrow aplasia.

What if the immune thrombocytopenia is secondary to other blood disorders?

While chronic lymphocytic leukemia and myelodysplastic syndrome would be very unlikely in our patient given her young age, other clinical conditions could be present, such as autoimmune lymphoproliferative syndrome and systemic lupus erythematosus. It has not yet been decided which tests should be performed to search for specific conditions, particularly if there are not specific symptoms or conditions suggesting a particular entity. We assay immunoglobulin levels and do thyroid tests in our patients, as we certainly did in this young woman. Ideally in the future there would be an established panel of tests for patients with putative ITP which would explore inherited thrombocytopenias, bone marrow failure, secondary ITP, other diagnoses that could resemble ITP such as myelodysplastic syndrome, markers of the future course of the ITP, the degree of bleeding, and to which treatments the patient would respond best.

What is the optimal second-line treatment for a young female with immune thrombocytopenia?

There are numerous options that can be considered in this non-pregnant premenopausal female (Table 1)

Rituximab

Rituximab and other (generic) anti-CD20 monoclonal antibodies exert immunosuppressive effects by depleting B lymphocytes. This occurs uniformly in the blood and bone marrow but what happens to B cells in lymph nodes is not well-defined. Women under the age of 40 years with a less than 2-year history of ITP usually respond to rituximab, with the response rate and especially the "cure" rate being high.[26] If our patient and her hematologist opt for rituximab, she would receive four infusions of 375 mg/m^2 weekly for 4 weeks. If she has a good response, close monitoring may not be needed. While studies have not de-

Table 1. Comparing second-line treatment options in non-pregnant premenopausal females.

Treatment options	Pros	Cons
Rituximab	High likelihood of good response in both short and especially long term (>50%)	Risk of first-infusion reaction which can be mitigated by steroids COVID vaccination not possible for 6-12 months Very rare risk of PML[45] Risk of hypogammaglobulinemia with rituximab + dexamethasone 10-20% with possible need for short-term IgG-replacement IVIG
TPO-RA: Eltrombopag Romiplostim Avatrombopag	Very high response rate (70-80%)	Risk of thrombosis (increased with OCP, underlying APLA, other prothrombotic causes) which usually occurs in 1st year of use Pain from headache-myalgia may occur Abnormal liver function, especially for eltrombopag which also needs very strict ingestion on empty stomach
Splenectomy	High long-term response rate (60-70%)	Risk of perioperative bleeding, VTE, intracellular infection, sepsis Need to vaccinate at least 15 days prior to surgery[88] Revaccination schedule unknown
Fostamatinib	Overall response 43% in first 12 weeks on treatment, time to response 15 days[47]	Side effects: hypertension, nausea-diarrhea, dizziness, ALT increases Clinically meaningful responses in patients with failure of splenectomy, TPO-RA and/or rituximab[45]
Immunomodulatory agents: azathioprine, mycophenolate mofetil, cyclosporine, dapsone, cytoxan	Many years of usage in some cases e.g., azathioprine, Attacks pathophysiology of autoimmune disease	Usually slow responses, which can take 1-3 months to develop without predictability Various individual toxicities: Cyclosporine - neurological and renal Azathioprine and danazol – liver abnormalities Danazol - facial hair and acne MMF-headache, gastrointestinal Dapsone - hemolysis

COVID: coronavirus disease 2019; PML: progressive multifocal leukoencephalopathy; IVIG: intravenous immunoglobulin; TPO-RA: thrombopoietin receptor agonist; OCP: oral contraceptive pills; APLA: anti-phospholipid antibody; VTE: venous thromboembolism; ALT: alanine aminotransferase; MMF: mycophenolate mofetil.

termined the optimal dose, 375 mg/m^2 once a week for 4 weeks is the most commonly used dosing regiman. The addition of dexamethasone to the rituximab may provide an extra “curative” effect via the former’s anti-plasma cell effect, although it also increases the risk of hypogammaglobulinemia. Administration of dexamethasone would reduce the first-infusion side effects of rituximab, and our patient could stop the steroid after one or two cycles if she does not tolerate it well instead of completing three cycles.

It is prudent to check immunoglobulin levels to rule out CVID and a hepatitis B panel prior to starting rituximab. The risk of coronavirus disease 2019 (COVID) and delayed vaccination are in addition to other potential side effects such as first-infusion reactions, serum sickness, and even the very rare possibility of progressive multifocal leukoencephalopathy. If dexamethasone and rituximab are combined, there is a 10-20% possibility of developing hypogammaglobulinemia which may necessitate IVIG for a few months even in patients who start out with normal immunoglobulin levels. Combining this problem with the issue of the patient being unable to undergo vaccination for COVID reduces the benefit/risk ratio of rituximab treatment substantially, despite its curative potential. If the coronavirus pandemic wanes, this may be less of a consideration.

If treatment with rituximab is delayed too long in this woman, the chance of “cure” may be reduced. Her immunoglobulin levels are normal and she does not have hepatitis B surface antigen, so the risks of aggravated hepatitis B and hypogammaglobulinemia are less substantial. Lucchini *et al.* provide more information on the place of rituximab treatment in ITP.[27]

Whether because of vaccination and/or infection, the current COVID pandemic is affecting ITP management and may have an impact on patients who are on second-line ITP treatment options. Guidelines on post-infection or vaccination ITP treatment are summarized in Table 2. Our patient should be vaccinated against SARS-CoV-2 at least 5-8 weeks before initiating rituximab in order to have time to receive and fully respond to both doses of Moderna and Pfizer vaccines. It might be optimal to wait a little longer

Table 2. Considerations regarding severe acute respiratory syndrome coronavirus-2 and second-line treatments for immune thrombocytopenia.

Second-line option	COVID Infection	SARS-CoV-2 vaccination prior to initiation of ITP second-line treatment	SARS-CoV-2 vaccination after ITP second-line treatment
Rituximab	Limited information on effects of rituximab during active COVID infection[89] Patients may be good candidates for administration of anti-SARS-CoV-2 antibodies via convalescent plasma or engineered monoclonal antibodies[44]	Vaccinations should be given prior to starting rituximab e.g. Moderna a minimum of 5 weeks prior, Pfizer a minimum of 6 weeks prior	If not vaccinated prior to starting rituximab, need to wait to be vaccinated until 6-12 months after completion of last rituximab dose[28]
TPO Agents	Risk of thrombosis[29]		
Fostamatinib	Potentially useful in COVID infections independent of platelet function[47]		
Immunomodulatory agents	Patients may be good candidates for administration of anti-SARS-CoV-2 antibodies via convalescent plasma or engineered monoclonal antibodies[44]	Vaccination is recommended at least 2-4 weeks prior to starting immunosuppressive agents[44]	If the patient is receiving or has received immunosuppressive therapy, consider vaccination 6 months after the patient has been taken off therapy to increase the likelihood of developing immunity[44]
Splenectomy *Recommend screening for COVID infection prior	Urgent administration of IV antibiotics is mandatory until bacterial cultures are documented as negative, even if the fever is attributed to proven or suspected SARS-CoV-2 infection[44]	Vaccination is recommended at least 2-4 weeks prior to the planned splenectomy[44]	Splenectomized persons and those who had received five or more prior lines of therapy were at highest risk of ITP exacerbation[29]

COVID: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; ITP: immune thrombocytopenia; TPO: thrombopoietin; IV: intravenous.

afterwards to sustain the vaccine effect. If the patient is not vaccinated prior to rituximab treatment, she will not be able to be vaccinated against SARS-CoV-2 for at least 6 if not 12 months;[28] this would also apply to a booster vaccination (Table 2). The vaccination might affect her platelet count although she is not in a high-risk group which includes those who have had a prior splenectomy and/or five or more lines of previous ITP treatment.[29] There is limited information on the risk of developing severe COVID in ITP patients undergoing rituximab therapy. In CVID and especially agammaglobulinemia patients, the ability to clear the SARS-CoV-2 virus may be limited, and a patient may remain polymerase chain reaction-positive for weeks or even months.

On the one hand, rituximab with dexamethasone seems a good treatment option because, if she responds well to the four weekly infusions, she can be checked relatively infrequently afterward. On the other hand, the effects on response to SARS-CoV-2 vaccination are clinically significant. There appears to have been a marked decrease in rituximab use in ITP since the onset of the COVID pandemic.

Other immunomodulators

Previously, immunomodulatory agents were widely used second-line treatments, but drawbacks include the need to wait 1-3 months for the platelet count to increase, side effects (depending on the agent) such as hepatic toxicity, and the need to take these medications consistently long-term.[5] If a single agent is used, the risk of infection despite the immunosuppression seems very small, but for these agents, efficacy is less than 50%. This group is lumped together as if all agents are the same; it potentially includes mycophenolate mofetil, danazol, dapsone, azathioprine, cyclosporine, and cyclophosphamide.

Recently, a randomized controlled trial of steroids given with or without mycophenolate mofetil within 1 week of the diagnosis of ITP showed that the “cure” rate was

higher in the combination arm.[30] One surprise was that quality of life was significantly lower among patients treated with the combination despite them having a better platelet response. Another surprise was that more than 50% of patients on the steroid-alone arm were cured despite a low rate of dexamethasone usage and that 27% of the patients were over 65 years of age. The study nonetheless highlighted the potential advantage of earlier use of second-line treatment.

There are at least 20 studies of danazol, almost all of which demonstrated a positive effect on platelet counts; this drug induces facial hair and acne and may be toxic to the liver. Dapsone, beyond an immunosuppressive effect, induces hemolysis which mimics IV anti-D; in patients with glucose-6-phosphate dehydrogenase deficiency, the hemolysis can be severe. Azathioprine has a long-standing history of use in ITP and a contributing safety base in pregnancy in patients taking it following kidney transplantation; it may cause hepatic toxicity in 1%. We reported on its combination with danazol, with good results in 13 of 17 difficult-to-treat patients.[31] Cyclosporine repolarizes cell membranes, which shuts down cell membrane pumps that extrude therapeutic agents from the cell. This may reinstate the effect of certain treatments e.g., steroids. Finally, cyclophosphamide can be given IV or orally. The best results appear to occur when using it IV in two or three infusions.[32] Mechanistic information supporting the use of cyclophosphamide is that it has anti-plasma cell effects and that it spares megakaryocytes and platelets. Cyclophosphamde does, however, have well-known substantial side effects: hematuria, bladder fibrosis, immunosuppression, and nausea and vomiting.

Thrombopoietin receptor agonists

Another option for second-line therapy would be a thrombopoietin receptor agonist (TPO-RA). The primary advantages of these drugs are the high response rate and low likelihood of induction of malignancy or other irreversible toxicity. The primary toxicity is development of venous and arterial thrombosis. If our young female patient were on birth control, there may be an added risk of thrombosis.

There are three TPO-RA currently available in the USA and Western Europe: romiplostim,[33] eltrombopag[34] and avatrombopag;[35] their efficacy and toxicity have been outlined in a recent review, including discussion of class effects such as headache, myalgia, and thrombosis.[36] The mechanisms of effect of these agents differ by where they bind to the thrombopoietin receptor, in RNA upregulation of transcription factors by romiplostim and eltrombopag,[37] and by the essential role of intracellular iron chelation by eltrombopag.[38] The clinical importance of these mechanistic differences is “confirmed” by “switch studies” in which one of romiplostim or eltrombopag was effective when the other was not.[39,40] Recent studies demonstrated that switching from one of these two TPO-RA to avatrombopag was also often effective.[29,41] Toxicity and efficacy do not differentiate the three agents substantially, although one article suggests that romiplostim maintains efficacy at higher endogenous thrombopoietin levels than does eltrombopag[29] and eltrombopag is thought to be associated with higher rates of transaminitis.[34,36]

Eltrombopag. Eltrombopag is an oral TPO-RA which requires a very empty stomach ideally 2 hours before and after taking it, which is intimately related to its requirement to chelate intracellular iron as an integral part of its mechanism of effect.[38] If eltrombopag has chelated calcium or iron during ingestion, it cannot chelate intracellular iron and will, therefore, be ineffective. Liver function tests must be monitored in patients taking eltrombopag, as hepatotoxicity is considered common (1-10%) and 3% of adults and children cannot tolerate eltrombopag for this reason.[36]

Romiplostim. Because romiplostim is injected subcutaneously weekly, there are no issues of absorption or doubts about compliance. There may be more cycling of the platelet count as compared to that with the oral TPO-RA, likely because of romiplostim’s weekly instead of daily administration. As with all the TPO-RA, making small changes in dosing will limit the likelihood of cycling. Development of antibodies, neutralizing and non-neutralizing, to romiplostim is more common in children than in adults;[44] however, these antibodies have surprisingly little effect on clinical efficacy for reasons that are not clear. Myalgia may be more common with romiplostim. As of writing, romiplostim can be self-injected by patients in Europe but not in the USA.

Avatrombopag. Avatrombopag, a second oral TPO-RA, has the least data describing its use. It is taken once daily using only tablets of 20 mg with dose ranges from 20 mg by mouth once a week to 40 mg (2 tablets) daily. There are very limited data on long-term usage. In one study, avatrombopag was associated with a 16.5% incidence of thrombosis but this was likely an artifact resulting from the small numbers of patient.[42] Two recent studies testified to the effect of avatrombopag in patients not responding to romiplostim and/or eltrombopag.[29,41] It is recommended that this TPO-RA is taken with food so that its absorption is more consistent.

There is much to recommend the use of a TPO-RA in our young woman.[43,44] There is no reason to suspect that such an agent would have an adverse impact on the clinical course of COVID if an infection were to occur although there may be an additive risk of thrombosis.[29] In the COVID pandemic, the oral agents would be preferred over romiplostim to lessen exposure to SARS-CoV-2 secondary to weekly attendance at an outpatient department. Local

laboratory counts and virtual visits lessen this risk for patients; home nursing visits for injections would do the same.

Fostamatinib

Fostamatinib is a first-in-class, orally active spleen tyrosine kinase (Syk) inhibitor indicated for the treatment of ITP. The primary studies underestimated its efficacy, probably because the median duration of ITP in the trial population was more than 8 years and in 47% of patients a TPO-RA had failed.[45,46] While the starting dose is 100 mg twice daily, 89% of responders increased to 150 mg twice daily. Long-term use and *in vitro* experiments have suggested that fostamatinib is anti-thrombotic but not pro-hemorrhagic because blocking Syk reduces signaling via the C-type lectin-like type II transmembrane receptor (CLEC2) and glycoprotein VI (GPVI) pathways. These two pathways have less redundancy in thrombosis than in control of bleeding. Fostamatinib is also thought to be anti-inflammatory and potentially useful in COVID, independently of any platelet effects.[47] On the other hand, of all approved second-line agents for ITP, it may be the least tolerable. It increases blood pressure in most recipients and there are relatively frequent gastrointestinal effects, including nausea with very occasional vomiting and the development of diarrhea; 5% of patients may develop transaminitis. There has not been evidence of increased frequency or severity of infections in association with fostamatinib use even though Syk is present in macrophages as well as in B cells and in other cells.

Splenectomy

The American Society of Hematology guidelines and international consensus report recommend that splenectomy be delayed to at least 1 year after the diagnosis of ITP, since the rate of resolution of ITP within the first 1-3 years of disease appears substantial even in adults.[4,5] Laparoscopic splenectomy is infrequently complicated by perioperative problems; response rates are initially 80% which relapse reduces to 60%. Late relapse beyond 2 years after splenectomy is very uncommon. Whether delaying splenectomy reduces its efficacy is a concern; a recent study from France[48] suggests that efficacy is maintained, and some patients responded better to TPO-RA after splenectomy.

There are long-term risks of adverse effects of splenectomy which are clinically significant, including not only overwhelming sepsis but also thrombosis, especially stroke. The risk of sepsis is based on less efficient blood stream phagocytosis and is exacerbated by low antibacterial antibody levels. Pneumococci are a more frequent cause of post-splenectomy sepsis than all other infections combined.[49] Following splenectomy, individuals also have an elevated risk of infections by encapsulated Gram-negative pathogens, e.g., *Capnocytophaga canimorsus* and *Bordetella holmesii*, as well as intraerythrocytic parasites, such as malaria and *Babesia*, as noted in a recent review of post-splenectomy infections.[50]

Providing patients appropriate and timely immunization for pneumococci, *Hemophilus influenzae B*, and meningococcus, antibiotic prophylaxis, education, and prompt treatment of infection mitigates this risk;[51] when to repeat pneumococcal and other vaccinations remains unclear. While vaccination appears more effective if given at least 2 weeks prior to splenectomy, vaccination can be administered after splenectomy if there is not time before the splenectomy or if vaccination would likely be ineffective because the patient is receiving high-dose immunosuppression or has recently received rituximab.

The risk of post-splenectomy thrombosis was not initially appreciated. Population studies using a Danish registry identified this risk, particularly with regard to stroke, with confirmation in other populations, e.g., the Nurses' Health Study.[52] Splenectomy for hemolytic anemias has been complicated by pulmonary hypertension, with mitigation by partial splenectomy and reduction in the use of splenectomy. Partial splenectomy may "hit the sweet spot" by reducing red blood cell phagocytosis but maintaining enough phagocytosis to prevent pulmonary hypertension and sepsis. The apparent absence of pulmonary hypertension after splenectomy for ITP suggests that partial splenectomy, like splenic embolization and radiation, is very rarely if ever used.

How we treated the young woman with immune thrombocytopenia

As this woman could not taper her prednisone successfully, still had bleeding, and had a platelet count <20x10^9/L, she met the criteria to receive a second-line treatment. After the considerations provided above and with her primary ITP, she opted for a TPO-RA which was based on her fear of COVID and need for vaccination and being in the first year of her disease. She chose to reserve rituximab, fostamatinib and immunosuppressives. She took a TPO-RA for a year and then was gradually able to discontinue it. She maintained a platelet count of 60-90x10^9/L on no treatment for several years without manifestations of bleeding. She was not troubled by fatigue or heavy menstrual bleeding.

Section II. Immune thrombocytopenia in pregnancy

Years later, our patient becomes pregnant.

What are the treatment considerations for our patient during pregnancy?

As ITP is common in women of reproductive age, it is not surprising that it may complicate the course of pregnancy. For pregnant women with known ITP, management changes throughout the course of pregnancy.[53] Figure 1 reviews treatment options available during each trimester, leading up to delivery and the post-partum period. In the first trimester of pregnancy, platelet counts may spontaneously increase, apparently because of the increased progestational hormones in the first trimester.[54] For this reason, relatively few women with ITP require treatment in the first trimester, which is fortunate from a teratogenic point of view. Risk of cleft palate from steroid use in the first trimester appears to be small.

In the second and especially third trimesters, platelet counts decrease even in healthy women without ITP, resulting in "gestational" thrombocytopenia.[55] Three large series suggest that the prevalence of gestational thrombocytopenia at the end of pregnancy is between 6.6% and 11.6%.[56-60] This has been attributed to increased volume of distribution in the later stages of pregnancy as well as "consumption". Recently, work from China presented at the 2021 European Hematology Association Congress hypothesized that very high estradiol levels towards the end of pregnancy inhibit platelet

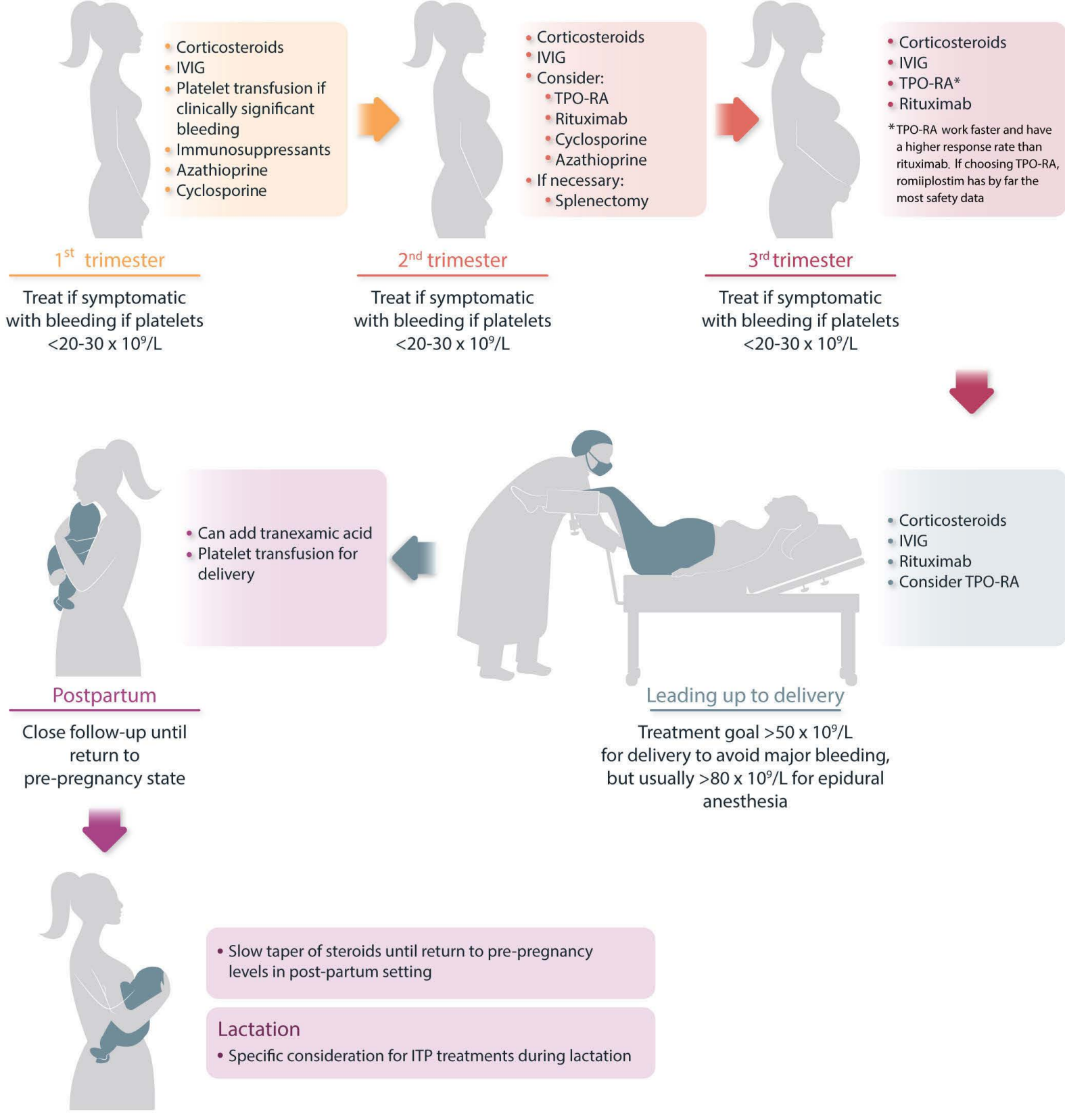

Figure 1. Treatment options for immune thrombocytopenia during pregnancy, leading up to delivery, and in the post-partum period. IVIG: intravenous immunoglobulin; TPO-RA: thrombopoietin receptor agonist; ITP: immune thrombocytopenia.

Table 3. Considerations regarding treatment options for immune thrombocytopenia during pregnancy.

Treatments (*Drug category*) Dosing regimen [FDA category]	**Considerations for mother**	**Risks to fetus**	**Evidence for use in pregnancy/ effect on lactation**
Prednisone (*Steroid*) 10-20 mg daily. Increase if necessary to 1mg/kg [C]	Usually the first agent to use Risk of diabetes, weight gain, acne, hypertension, osteoporosis,	Very low risk of cleft palate from steroid use in first trimester(53).	Very low concentrations in maternal milk and without biological effect[90]
Dexamethasone (*Steroid*) High dose, 40 mg per day x 4 days [C]	Low cost, ease of administration	Dexamethasone can cross the placenta. Slight increased risk of premature rupture of fetal membranes and abruptio placentae.	50% response[64]
IVIG (*Intravenous immunoglobulin*) Standard dose 400-1000 mg/ kg/day for 1-5 days	Can be given first line, Initially good response but often decreases with repeated use Aggravates fluid retention and hypertension Can be used to increase platelet counts initially while awaiting low dose prednis(ol)one Can be used for delivery but needs to be scheduled (timed rupture of membranes) Can worsen pregnancy-associated headache, malaise, infusion reactions, aseptic meningitis, fluid overload		Very low concentrations in maternal milk and without biological effect[90]
Rituximab (*Monoclonal antibody*) 375 mg IV/ weekly x 4 [C]	Use only for very severe cases[5]	Can cross placenta like any IgG Risk of B-cell depletion in neonates, perinatal and neonatal immunosuppression and subsequent infection	40-60% response rate within 1-8 weeks[66]
Anti-RhD (*Blood group RhoD antibody*) IV 50-75 µg/kg [C]	Can be used in refractory cases Risk of hemolysis and anemia Less expensive, shorter infusion time than that for IVIG	Risk of neonatal jaundice, anemia, and direct antiglobulin test positivity Given routinely for HDFN prophylaxis but at 1/10th the ITP dose	>70% of cases in a small series (n=8)[67]
Azathioprine (*Immunomodulator*) Variable dosing [D]	Increased risk of preterm birth	Can cross placenta, noted to have increased prematurity rate, lower birth weight, IUGR. No malformation risks across several studies Immune impairment reported in some exposed infants[69]	Several studies and large case series following renal transplantation, for autoimmune conditions[68] Compatible with lactation

continued on following page.

Cyclosporine (*Immunomodulator*) Variable dosing [C]	For refractory cases No significant toxicity to mother or fetus when used in pregnancy for inflammatory bowel disease, possible increased risk of preterm birth	Increased risk of IUGR[70]	No published experience in ITP in pregnancy, but used for inflammatory bowel disease[91] Present in breast milk
Romiplostim (*TPO-RA*) [FDA category not assigned]	Risk of maternal thrombocytosis Increased risk of VTE		Case reports with safety data from women with ITP in pregnancy[73]
Eltrombopag (*TPO-RA*) Start at 25-50 mg PO daily and increase as needed [C]	Very limited data requires a very empty stomach (ideally 2 hours before and after taking it), elevated liver enzymes		Case reports in pregnancy If in breast milk, potentially may be neutralized by calcium
rhTPO [FDA category not assigned, available in China]	No overt maternal toxicity	Infants followed until 1 year did not have any side effects	70% response rate with increase in maternal platelet count in 33 pregnancies[72]
Splenectomy (na) For refractory ITP or if significant toxicity with other therapies	Risk of perioperative bleeding, VTE, opportunistic infection, miscarriage, preterm labor and preterm premature rupture of membranes Need to be vaccinated at least 15 days prior to surgery[53]	Risks to fetus least in second trimester. Minimal data Transplacental passage of circulating maternal antiplatelet antibodies and the risk of neonatal thrombocytopenia are not affected by splenectomy	88% response rate Few complications in second trimester when least risky to fetus and uterine size may not complicate procedure[92]
Tranexamic acid [B, post-partum setting only]		Can reduce the amount of blood loss after delivery, reduces blood transfusion requirements. Low risk of post-partum thrombosis, PE reported in two cases[62].	Used only post-partum. Avoid antepartum due to potential risk of clotting of the placenta

Note on FDA pregnancy categories: (prior to 2015). Category B: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Category C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category D: there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. FDA: Food and Drug Administration; IV: intravenous; IVIG: intravenous immunoglobulin; HDFN: hemolytic disease of the fetus and newborn; ITP: immune thrombocytopenia; IUGR: intrauterine growth restriction; TPO-RA: thrombopoietin receptor agonist; VTE: venous thromboembolism; PO: *per os*; rhTPO; recombinant human thrombopoietin; na: not applicable; PE: pulmonary embolism

production.[61] While requiring confirmation, this hypothesis fits with both platelet counts falling and cases of ITP in pregnancy becoming progressively more difficult to treat with steroids and IVIG. Fortunately, there is rarely clinically significant bleeding in pregnant women with ITP unless the platelet counts become very low; one exception may be subchorionic hematomas.

Tranexamic acid can be used after delivery to reduce blood loss in this period and thus reduce blood transfusion requirements. The risk of postpartum thrombosis seems very low, although pulmonary emboli have been reported in two cases.[62]

Steroids in pregnancy

The standard treatments for ITP during pregnancy are steroids and IVIG (Table 3) which are the most widely used and felt to be the safest. The prednis(ol)one recommendation for ITP in pregnancy, because of the limited duration of anticipated treatment, is relatively low-dose prednisone (e.g., 10-20 mg daily) based on targeting a platelet threshold of 20-30x10^9/L. Prednis(ol)one often exacerbates physiological changes of pregnancy e.g., hyperglycemia, hypertension, and fluid retention; dexamethasone is to be avoided because of its fetal effects. If this lower dose of prednisone is successful, it avoids the risks of long-term high-dose steroids for the mother. Little to no prednisone enters the fetus because of placental β-11-hydroxylase.[63]

WIntravenous immunoglobulin in pregnancy

IVIG is effective; however, it must be given often e.g., biweekly so steroids are the recommended treatment. One study suggests that both steroids and IVIG are slightly less effective in pregnant women.[64] Overall, whether the efficacy of IVIG and prednis(ol)one in pregnancy is maintained becomes more important later in pregnancy. Patients who are difficult to treat require higher and higher doses of prednisone and more and more frequent IVIG dosing as pregnancy progresses.

The treatment of fetal and neonatal alloimmune thrombocytopenia has provided safety information that may be extrapolated to ITP. 'Aggressive intrapartum treatment' exceeds that of the treatment of ITP by including IVIG 1-2 g/kg/week and prednisone 0.5 mg/kg/day for many weeks. The apparent safety of these very high doses helps to assuage concerns regarding their use in ITP.[65]

Even with less severe ITP, preparing for safe delivery often involves intervention to undergo epidural anesthesia, for which the platelet count is often "required" to be greater than 80x10^9/L. The requirements for spinal anesthesia may not be as strict and are more variable than they are for epidural anesthesia. Even in a patient who responds well to IVIG and prednis(ol)one combination treatment, a platelet count of 80x10^9/L or higher is often achieved for only 2-5 days. If these treatments are relied upon, scheduling elective delivery is crucial so that administration of IVIG can be timed to achieve its optimal effect. The patient could either undergo a Caesarian section or have her membranes ruptured so she enters labor at the desired time. An amniocentesis may be required to assess fetal lung maturity.

Rituximab in pregnancy

In one study of 231 pregnancies with maternal exposure to rituximab for treatment of autoimmune cytopenias and other autoimmune disease, few neonatal infections were seen among the exposed neonates.[66] Hypogammaglobulinemia will not be present at birth if the mother does not herself have low IgG levels; however, it may manifest at 2 to 4 months of age if there is a persistent absence of infant B cells. Women are encouraged to avoid pregnancy for more than 4-6 months after rituximab exposure to prevent transmission of the rituximab to the fetus.[66] As shown in Figure 1, we believe that rituximab can be used in patients who do not respond well to steroids and IVIG.

Intravenous anti-D, azathioprine, cyclosporine, and splenectomy in pregnancy

Eight patients were treated with IV anti-D (WinRho) with reasonable efficacy and fetal safety;[67] no cases of neonatal anemia or hyperbilirubinemia were seen. Azathioprine has been extensively used in women who have undergone renal transplantation and become pregnant.[68] The registry of these patients suggested that azathioprine is relatively safe during pregnancy, but azathioprine takes 1-3 months to increase the platelet count. Infants of mothers taking azathioprine are noted to have an increased prematurity rate, lower birth weight, and intrauterine growth restriction; no malformations were seen. Immune impairment was reported in some exposed infants.[69] The effects of cyclosporine in pregnant women with ITP appear to be like those of azathioprine: reasonably effective, slow in onset, and with limited fetal risk. Experience of cyclosporine use in pregnant women has also been gained in the post-transplantation setting.[70] Mycophenolate is contraindicated in pregnancy.[71] If splenectomy is required, it is recommended that it be performed in the second trimester because the risk to the fetus is less than in the first trimester and the size of the uterus will be less obstructive than in the third trimester. Experience consists of isolated case reports.

Thrombopoietin receptor agonists in pregnancy

A major recent development affecting ITP in pregnancy is the use of thrombopoietin agents. Three sets of evidence for the use of thrombopoietin agents in pregnancy exist beyond scattered case reports. One study used re-

combinant human thrombopoietin (rhTPO, available in China) and evaluated 33 pregnancies in 31 women with ITP in pregnancy who did not respond to or relapsed after an initial response to prednisone.[72] Seventy percent of the women responded to rhTPO with an increase in the maternal platelet count and no overt maternal toxicity. Importantly, the babies, followed until 1 year of age, did not have any identified side effects of rhTPO treatment. A follow-up compilation of ITP cases explored 13 pregnancies in 12 women, including one who delivered a pair of twins, in whom a TPO-RA was used.[73] Usage of TPO-RA was divided equally between eltrombopag and romiplostim and both agents appeared effective and safe. Third, a safety surveillance program report of use of romiplostim in 186 women with ITP who received romiplostim during pregnancy indicated that in over 50 pregnancies with known pregnancy outcomes and in over 50 pregnancies with known birth outcomes, romiplostim appeared safe.[74] There were 12 births with thrombocytopenia requiring treatment, consistent with the maternal ITP; all were discharged home with eight having their thrombocytopenia resolved pre-discharge. Although limited by incomplete information, 75 women were exposed to romiplostim in the first trimester because of having been treated with romiplostim at the time they became pregnant. From the over 150 pregnancies for which any data were available, five infants had some kind of adverse finding: one had cytomegalovirus infection, one had unilateral inguinal hernia, one had a single umbilical artery with no other findings reported, one child was normal at birth but at the age of 2 was identified as autistic and one infant, whose mother received only one dose of romiplostim in the third trimester, had trisomy 8.

In summary, according to three reports of the use of three different thrombopoietin agents in pregnancy, these drugs appear to be safe as a class with no information available for avatrombopag, very limited information for eltrombopag, and considerable safety but little efficacy information for romiplostim. While efficacy is likely to be preserved in the mother, it is not known whether transplacental passage of these agents increases the neonatal platelet count. Our conclusion is that a thrombopoietin agent should only be used when the benefit outweighs the risk. However, if a thrombopoietin agent is considered in the third trimester, the available data strongly suggest that romiplostim is safe for the fetus (Figure 1, Table 2).

After scheduled vaginal delivery, our patient does well as does her baby. She breastfeeds but her newborn has persistent thrombocytopenia with platelet counts down to 30 x 10^9/L. She is prompted to stop breast feeding and, upon doing so, the infant's platelet count rapidly increases to normal. The mother's platelet count also return to its pre-pregnancy level and all treatment can be stopped.

Section III: Second-line treatment of immune thrombocytopenia in an older male patient

What if instead of a young woman in her early 20s, our patient is a 63-year-old male?

This patient is generally healthy but slightly overweight and had his gall bladder removed without incident 6 years ago. He has taken daily losartan, atorvastatin, and a baby aspirin for several years. Upon presentation with bruises, petechiae and profuse bleeding from his gums when he brushes his teeth, he is told to stop his aspirin. He is given dexamethasone 40 mg/day for 4 days and a single dose of IVIG 1 g/m^2/kg because of the aspirin. His platelet count increases dramatically within 2 days.

What diagnostic considerations are important here? First, as with the young woman, ITP must be distinguished from other thrombocytopenias; these are common in the elderly but different from those in a young woman. Autoimmune diseases such as systemic lupus erythematosus are much less likely, as are inherited thrombocytopenias. CVID is possible at any age but in addition to assaying serum immunoglobulins, serum protein electrophoresis to look for monoclonal proteins is appropriate. Other congenital immunodeficiency diseases are less likely, but lymphoproliferative diseases are more common. Chronic lymphocytic leukemia and non-Hodgkin lymphoma are both B-cell diseases associated with ITP. A blood smear may show too many small mature-looking lymphocytes; if T- and B-cell studies are performed, they would reveal too many B cells. Clonal hematopoiesis of indeterminate potential might occur but it is not clear what this condition would portend assuming the clonal cells do not reflect an overt malignancy. Preliminary information suggests that clonal T-cell populations may mediate refractoriness.[75] Ultrasound and/or computed tomography scans to look for malignancy may be indicated.

An important cause of thrombocytopenia in elderly patients is myelodysplastic syndrome. A bone marrow examination is necessary to diagnose this condition. Typically, marrow will be hyperplastic, but marrow cells will be undergoing apoptosis and not producing mature blood cells and reveal dyspoiesis. Diagnostics have improved remarkably as has clinical discrimination of different subtypes of myelodysplastic syndrome. Nonetheless. cases of myelodysplastic syndrome early in their evolution may be difficult to distinguish from "difficult" ITP.[76]

Drug-induced thrombocytopenia is a possibility since older patients may be taking more medications. Limited laboratory testing is available to demonstrate that thrombo-

cytopenia is drug-induced. Diagnosis generally relies on recognizing medications likely to cause thrombocytopenia; one approach is to change medications if any are newly initiated. Viral infections could also occur in this population e.g., hepatitis C, cytomegalovirus.

Patients over the age of 60 are thought to have a higher likelihood of fatal and non-fatal serious bleeding compared to younger patients;[77-79] recent studies of intracranial hemorrhage have supported earlier findings demonstrating a higher risk in those above 60 years of age. Thus, it may be appropriate to pursue an aggressive approach in this patient, such as the addition of IVIG to steroids.

Which second-line treatment is optimal for a 63-year-old male?

Rituximab in an older male

In this case of ITP, the older man has a reasonable likelihood of a response but, even if he responds well, his response will very likely last only 6-12 months. The chance of a long-term (>1 year) response is low. Furthermore, as discussed previously, after rituximab it would not be possible to vaccinate the patient against SARS-CoV-2, which is important since this 63-year-old is in a high-risk group and would benefit from boosters. As indicated, there is a 10-20% possibility of developing significant hypogammaglobulinemia when the combination of dexamethasone with rituximab is used.[26] A good initial response followed by the expected relapse would allow rituximab to be reused, but it remains unlikely to lead to a cure[80] and the probability of hypogammaglobulinemia occurring is thought to increase with repeated use.

Splenectomy in an older male

Splenectomy is used even less in this age group, since efficacy is lower, and the risk of side effects is higher. The results of splenectomy are less successful in older patients with ITP, but there is no clear age at which this effect occurs.[81] In addition, there may be a higher risk of peri-operative complications and post-splenectomy thrombosis in this older patient. One could take a risk-based approach to splenectomy for this 63-year-old by considering the comorbidities and proceeding if he has few to no comorbidities.

Thrombopoietin receptor agonists in an older male

Another second-line therapy is a TPO-RA. The primary advantages remain the high response rate and the low likelihood that there will be major side effects although venous and arterial thrombosis would be the primary concerns in this older man. It is important to fully assess the risk of thrombosis looking at risk factors such as obesity, family history, and personal history.[53] The use of thrombopoietin agents would be similar in both patients and is described in the package inserts and a recent review.[36]

If romiplostim is chosen, we would initiate treatment with 3 μg/kg/week and increase by 2 μg/kg/week until the platelet count rises above 30-50x10^9/L. In more practical terms, this could mean whole vials of 250 and 500 micrograms which are almost universally available; if smaller and larger vial sizes are/become available this would allow more precise weight-based dosing. If a sufficient platelet count is achieved, it is important not to change romiplostim doses too quickly, i.e., not more than 1 μg/kg/week. This minimizes cycling of platelet counts and prevents them from going too high or falling too low. If the platelet count goes very high (with any of the 3 TPO-RA), do not withhold the dose, but decrease it by 1 μg/kg (or equivalent); several days of aspirin can be given if there is concern of thrombosis.

If eltrombopag is chosen, the starting dose is 50 mg by mouth daily; lower doses might be required in East Asian patients. If the count does not increase sufficiently within 1-2 weeks, increase the dose to 75 mg daily. If the count increases too much, decrease the dose to 25 mg daily. The maximum change would be 25 mg/daily once a week. If none of the doses allows for a stable count of 50-100x10^9/L, then alternating doses might be preferred e.g., 50 mg on odd days and 75 mg on even days. As discussed, eltrombopag must be taken on an empty stomach. In our experience, the best approach is to eat dinner, not eat after the end of dinner and then take the eltrombopag with water at bedtime, at least 2 hours after dinner. If this gentleman urinates every night, this could be a time to take eltrombopag.

If avatrombopag is chosen, the starting dose is 20 mg daily. The dose could be adjusted to as high as 40 mg daily or as low as 20 mg on one day per week. There is only one size of avatrombopag tablet, i.e. 20 mg. The tablet is taken once daily and there are no dietary restrictions. As with the other agents, dose changes should be limited in magnitude and not performed more often than weekly.

With all three agents, it is not clear how/when to taper and attempt to discontinue treatment. A recent study demonstrated a greater than 50% successful discontinuation rate when at least 2-3 months of stable TPO-RA dosing, no bleeding, and a platelet count >100x10^9/L were required for the discontinuation attempt.[82] Patients were on romiplostim a median of 12 months before tapering; the doses administered were higher than normal to obtain stable counts >100x10^9/L. The tapering protocol was at 2-weekly intervals for a total of not more than 2 months of tapering. It remains unclear how often a patient who has required a thrombopoietin agent for 2 or more years will be able to discontinue treatment. Other studies have suggested an approximately 20-25% rate of successful discontinuation in the first year.

Fostamatinib in an older male

If this patient were at particular risk of thrombosis, fostamatinib might be a particularly good option. Otherwise, in

general practice, it is usually reserved for patients who have failed to respond to thrombopoietin agents.

With many second-line agents, there are various treatment options and courses depending on individual responses, relapses and potential complications with each agent, as demonstrated in Figure 2.

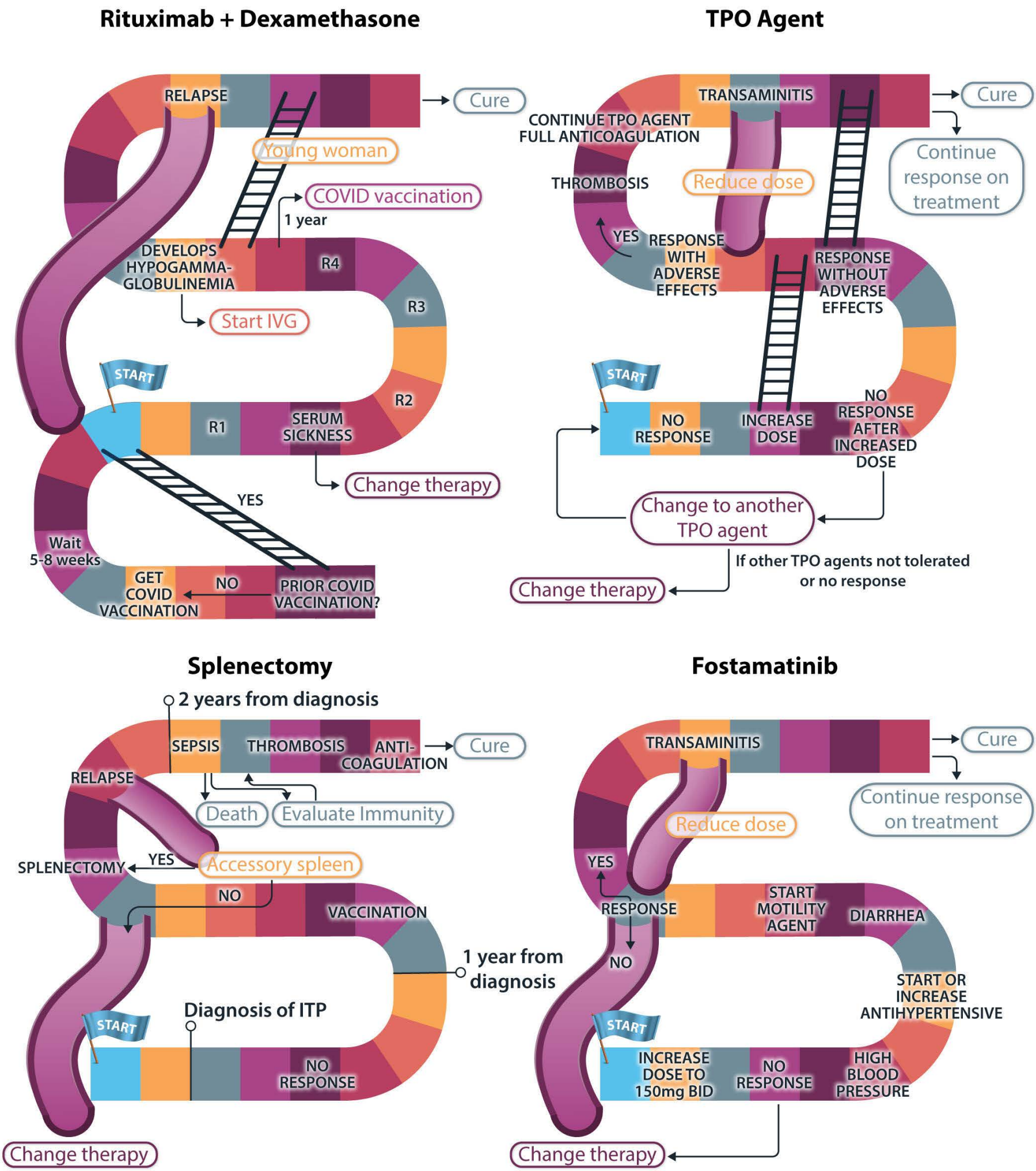

Figure 2. Second-line treatment options for immune thrombocytopenia and possible treatment courses. TPO: thrombopoietin; R1, R2, R3, R4: first, second, third and fourth weekly dose of rituximab; COVID: coronavirus disease 2019; ITP: immune thrombocytopenia; BID: *bis in die*.

Section IV: Third-line therapy for immune thrombocytopenia and beyond

What happens if the thrombopoietin agent used in the two patients does not work or at least cannot be tapered?

In the case of the young woman, the platelet count remained less than 20x10^9/L and the young woman had heavy menses, bruising and nosebleeds. The now 26-year-old woman opted for rituximab. She had a long-term response but unfortunately relapsed after 4 years. She considered repeating the rituximab and undergoing splenectomy but opted to try a different thrombopoietin agent since she was not planning another pregnancy in the immediate future. Previously she used eltrombopag so she now tried avatrombopag. On a dose of 20 mg/day she was able to maintain an adequate platelet count and is very slowly tapering her dose. This choice was consistent with evidence that not responding well to one TPO-RA does not preclude good response to another.

Our older, male patient, given his continued bruising and minor nosebleeds, was afraid of major bleeding; he also felt very tired even though he was not anemic. The now 64-year-old man opted to try rituximab since avatrombopag did not work well for him. He received the standard dose of rituximab with dexamethasone. He responded which a platelet count of 60x10^9/L by 6 weeks after initiating treatment; however, his count started to fall monthly down to 30x10^9/L. He and his doctor decided to initiate mycophenolate mofetil and he began with a dose of 500 mg twice daily and then increased to 1000 mg twice a day. He tolerates this treatment well and his platelet counts remain around 40-50x10^9/L.

Thus, both patients needed treatment. Some patients with low (not very low) platelet counts who have no bleeding or other issues e.g., need for anticoagulants or fatigue, may not require treatment. Avoiding treatment is always optimal if this does not jeopardize quality of life.

What if none of the obvious options (thrombopoietin agents, rituximab, splenectomy) helps and no single treatment, including fostamatinib and mycophenolate mofetil is effective?

It is difficult to predict what approach will be effective in these "refractory" patients. If a patient has been on too low a dose or for too short a period, it may not be clear that a given medication will not be helpful.

The approach to difficult-to-treat patients, such as these examples, is discussed at great length in our review of refractory ITP and in another recent review.[1,83] The major principles are: (i) spend time reconfirming the diagnosis; reconsider all options if response to treatments of ITP is absent or very limited: (ii) do a complete bone marrow examination, unless one was performed recently, with aspirate, biopsy, flow cytometry, and cytogenetics; (iii) if a treatment is ineffective, continue the treatment and add another treatment initiating combination therapy. In our opinion, this is preferable to discontinuing the ineffective treatment and starting another one; (iv) if indeed the case is refractory ITP, combination approaches are often better than single treatments. Including treatments with different mechanisms of effect is useful; however, there are situations in which two agents targeting the same mechanism are effective such as combining IVIG and IV anti-D;[31] and (v) when using combination treatments, it would be ideal to not give maximum doses and to select agents with differing toxicities. If an adverse event requiring a change in treatment occurs, it is then easier to choose the agent to stop and/or replace. In our review of published reports,[1] a TPO agent was often a crucial component of combination treatments.

In difficult patients, the inability to define the pathogenesis in most cases makes the treatment selection blind. Fortunately, multiply refractory patients for whom no treatment seems to bring their platelet count up at all are very rare. More commonly at least one treatment will transiently increase the platelet count. This minimizes the chance of serious bleeding and creates an approach for ongoing management, although continued steroid overuse must be avoided.

Section V. Agents currently under study

What are the experimental agents which are likely to be available in the future?

Various experimental agents for ITP are being studied and other drugs, currently used for other conditions, are now undergoing trials in ITP. It is uncertain whether, and if so in what context, any or all these agents will ultimately have a major role in the management of ITP. On the one hand, they could be more effective and less toxic than currently used agents and have specific areas of efficacy based on their unique mechanisms of effect. On the other hand, they might be redundant, have toxicities, and not provide substantial additional value.

FcRn inhibitors

The putative mechanism of effect of FcRn inhibitors is reduction of antiplatelet IgG levels by inhibition of "normal" IgG recycling. IgG levels fall dramatically with FcRn inhibition, and it is thought that the IgG anti-platelet antibody levels fall at least as much, resulting in less platelet destruction and greater platelet production. Efgartigimod and rozanolixizumab have gone through phase II studies; the results were published in 2020 and both studies demon-

strated more than 50% acute platelet responses.[84,85] Both agents are in ongoing phase III trials which, like many studies, were slowed by the COVID pandemic. Since FcRn inhibition does not lower IgA and IgM levels nor does it affect T-cell or macrophage function, trials have not been complicated by the development of infections despite very low IgG levels being reached. Nonetheless, there is concern that IgG levels below 200 mg/dL (lower limit of normal: 639 mg/dL) may be dangerous. With one FcRn inhibitor, albumin levels were lowered, and cholesterol increased; FcRn also recycles albumin.

Active studies of FcRn inhibitors include treatment of myasthenia gravis, pemphigus vulgaris, hemolytic disease of the fetus and newborn, and antibody-mediated neurological diseases. In the phase III studies, the FcRn inhibitors are being administered weekly by subcutaneous administration with the goal of eventual home administration.

Bruton tyrosine kinase inhibitors

The most widely used Bruton tyrosine kinase (BTK) inhibitor is ibrutinib for chronic lymphocytic leukemia and non-Hodgkin lymphoma with excellent results in treating these entities; anecdotally, several thrombocytopenic patients with chronic lymphocytic leukemia had substantial platelet improvements. Thus, it was natural to think of BTK inhibition for B-cell diseases like ITP. However, ibrutinib was found to lead to serious bleeding in about 1% of cases, an effect that was subsequently suggested to be caused by inhibition of collagen-platelet interactions. Newer BTK inhibitors, e.g., rilzabrutinib, designed to allow normal platelet function for patients with ITP, have been effective in ITP in phase II trials, with a 50% response rate seen at the top dose, 400 mg twice a day.[86] As was seen in trials with fostamatinib and FcRn inhibitors, the patients enrolled have been heavily pretreated with long-term histories. It is highly likely that BTK inhibitors will inhibit response to SARS-CoV-2 vaccination.

Complement inhibitors

Studies of complement pathway inhibitors in ITP would have begun years ago if the cost of the Alexion anti-C5 monoclonal antibody (eculizumab) had not been so enormous. Early results of C_1S inhibition are impressive but still preliminary. This strategy has yielded good results in cold agglutinin disease, demonstrating its biological effect on the complement system which is translated into clinical hematologic efficacy.

Conclusions

What would we have liked to have been able to offer our two patients with immune thrombocytopenia?

First, it would have been nice to have been able to predict their course including many factors: risk of bleeding, likelihood of chronicity, which treatments would be most effective, and which most toxic.

Second, it would have been nice to have a curative but nontoxic treatment to offer. We discussed the use of rituximab in a younger woman as there is good likelihood of cure in a patient of this age and gender. But in other patients, there is very little likelihood of cure and in her case, vaccination for SARS-CoV-2 was a problem. This leaves splenectomy which is remarkably effective; recent work suggests that it remains effective even in patients who have been treated with thrombopoietin agents.[48] Why are patients so unwilling to undergo splenectomy? Perhaps the primary reasons are the inability to know whether a patient will get better on their own, whether the splenectomy will be successful, and the irreversibility of it. Furthermore, post-splenectomy risks of sepsis and thrombosis continue lifelong. In the future, use of combinations of agents (dexamethasone and rituximab, steroids and mycophenolate mofetil, dexamethasone and eltrombopag, or others) within 1 week of diagnosis may provide a higher level of cure and justify the extra expense and higher risks of these interventions.

Finally, treatment selection could be more rational if data were provided by randomized, controlled trials comparing agents and regimens. To date, all the randomized controlled double-blind trials of second-line agents have involved comparison of a treatment to placebo. We are not aware of any trials comparing one second-line agent to another, although Chinese hematologists have recently compared a given agent to the same agent plus a second agent. Examples include rituximab with and without thrombopoietin, and dexamethasone with and without eltrombopag. More of these studies are urgently needed.

In summary, it is not possible to have a “one size fits all” approach to ITP. Rather we have tried to emphasize that individualizing treatment is important and should include shared decision-making. The optimal choices vary with gender and age and the COVID pandemic has an impact as well. As additional information is accrued, management in certain situations may be clarified but there is a long way to go to achieve for ITP what we all take for granted in the evidence-based management of leukemia.[87]

Disclosures

JBB is a consultant or on an advisory board for Amgen, Novartis, Sobi, Rigel, UCB, Argenx, Sanofi, Astra-Zeneca, Pfizer, and CSL-Behring; and is a member of a Data and Safety Monitoring Board for UCB, CSL-Behring. CAG has no conflicts of interest to disclose.

Contributions

JBB and CAG wrote and edited the manuscript and both agreed to its submission for publication.

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