CLINICAL PRACTICE

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Immune Thrombocytopenia

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 72-year-old woman who is receiving apixaban for atrial fibrillation but otherwise does not have a clinically significant medical history presents to the hospital with lower gastrointestinal bleeding. On admission, her hemoglobin level is 8.5 g per deciliter, platelet count 2000 per cubic millimeter, and white-cell count 5300 per cubic millimeter. She receives a transfusion of packed red cells and platelets that results in an increase in the hemoglobin level and a decrease in bleeding, but only a transient increase in the platelet count. The examination is unremarkable. A peripheral-blood smear shows no abnormalities other than thrombocytopenia; these findings are consistent with a diagnosis of immune thrombocytopenia. How should this case be managed?

THE CLINICAL PROBLEM

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by isolated thrombocytopenia. Patients may be asymptomatic at presentation or they may present with mild mucocutaneous to life-threatening bleeding. Although only 5% of patients with ITP present with severe bleeding,[1] bleeding leading to hospital admission within 5 years after diagnosis develops in approximately 15%.[2] Irrespective of bleeding problems, patients with ITP often report fatigue and impaired health-related quality of life.[3] The risk of venous thromboembolism is twice as high among patients with ITP as among persons in the general population; the management of venous thromboembolism may be especially problematic given the concomitant risk of bleeding.[4]

ITP may be a primary condition or it may be caused by other diseases. The differential diagnosis of thrombocytopenia and the potential secondary causes of ITP are outlined in Table 1. Overall, the incidence of ITP ranges from 2 to 4 cases per 100,000 person-years, with two peaks: one between 20 and 30 years of age with a slight female predominance and a larger one after 60 years of age with equal sex distribution.[5,6] Although some patients have one episode of ITP followed by an immediate remission, chronic ITP develops in up to 70% of adults with this condition. Both spontaneous and treatment-induced remission can occur many years after diagnosis.

The pathophysiology of ITP is complex and remains incompletely understood (Fig. 1). The traditional concept is that antibody-coated platelets are prematurely destroyed in the spleen, liver, or both through interaction with Fcγ receptors.[7] Autoantibodies can also induce complement-mediated or desialylation-induced

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KEY CLINICAL POINTS

IMMUNE THROMBOCYTOPENIA

- Immune thrombocytopenia (ITP) is diagnosed in patients with a platelet count below 100,000 per cubic millimeter in whom other causes of thrombocytopenia have been ruled out.
- Patients with ITP who present with serious bleeding typically receive platelet transfusions, glucocorticoids, and intravenous immune globulin.
- In patients with no bleeding or nonserious bleeding, treatment decisions are guided by the patient's platelet count, age, coexisting conditions, and preference.
- Glucocorticoids are used as first-line treatment, but prolonged use should be avoided owing to adverse effects.
- For patients in whom ITP does not remit or relapses soon after glucocorticoid treatment, other medications for which there are high-quality data include thrombopoietin-receptor agonists and rituximab.
- Splenectomy is not recommended during the first year after diagnosis of ITP unless medical treatment is not available; otherwise, it is reserved for patients with ITP that is refractory to medical treatment.

destruction of platelets,[8,9] as well as inhibit megakaryocyte function.[10] However, antiplatelet antibodies are not detected in up to 50% of patients; this raises the possibility of alternative mechanisms of platelet destruction. Abnormalities in T cells have been described, including skewing of T helper (Th) cells toward a type 1 helper T (Th1) and type 17 helper T (Th17) phenotype[11] and a reduction in the numbers and function of regulatory T cells,[8,12] which could drive the autoimmune process. Limited studies suggest that CD8 cells are also involved.[13]

STRATEGIES AND EVIDENCE

DIAGNOSIS

ITP is defined as a platelet count below 100,000 per cubic millimeter in patients in whom other causes of thrombocytopenia have been ruled out.[14] A clinical history, including assessment of the use of drugs, physical examination, and complete blood count, is important to rule out other causes of thrombocytopenia and to evaluate for secondary causes of ITP (Table 1). Examination of the peripheral-blood smear in a patient with ITP shows reduced numbers of platelets with no other abnormalities (e.g., schistocytes and dysplastic changes); although some patients have large platelets, this is not a pathognomonic feature (Fig. 2). There is no diagnostic test for ITP; antiplatelet antibodies are detected in only 50 to 60% of patients with ITP and measurement of such antibodies is not recommended in the diagnostic workup.[15,16] Bone marrow examination is not diagnostic in patients with ITP and is performed only in those with other hematologic abnormalities and in those who do not have an adequate response to treatment.

TREATMENT

Treatment of Active Bleeding

The current goals of treatment are to stop active bleeding and reduce the risk of future bleeding.[15,16] If the patient has active serious bleeding, urgent treatment is indicated. Specific measures, where appropriate, include the withdrawal of anticoagulant and antiplatelet agents and treatment with platelet transfusions, glucocorticoids, intravenous immune globulin (IVIG), or all of these measures; data from randomized trials are lacking, and the use of these treatments is supported generally by small observational studies.

Platelet transfusions can help to limit bleeding, but they have only transient effects (for a few hours), and therefore the patient may need to undergo transfusions repeatedly. They should not be used alone but rather in combination with IVIG and glucocorticoids.[15]

IVIG raises the platelet count within 1 to 4 days in 80% of patients, but effects last only 1 to 2 weeks.[15] IVIG is indicated in patients with active serious bleeding and in those with very low platelet counts (<10,000 per cubic millimeter), who are at increased risk for serious bleeding.[17] Concomitant use of glucocorticoids with IVIG can be associated with a more sustained response than that with IVIG alone.[16,18]

In life-threatening situations, additional treatments may be required. Antifibrinolytic treatment (tranexamic acid) can help to stop bleed-

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Table 1. Differential Diagnosis and Secondary Causes of Immune Thrombocytopenia (ITP).*

Variable	Clinical and Laboratory Findings	Other Tests and Findings to Confirm Diagnosis
Differential diagnosis of ITP		
Pseudothrombocytopenia	No symptoms, in vitro phenomena	Platelet aggregation on peripheral-blood smear, repeat platelet count in citrated blood
Renal or liver disease	Symptoms, signs, and clinical history	Renal function and liver-function tests and imaging of abdomen, including liver and spleen
Myelodysplastic syndrome, acute leukemia	Other cytopenias and abnormal peripheral-blood smear	Peripheral-blood smear, bone marrow aspirate and biopsy, with flow cytometry and cytogenetic testing
Aplastic anemia	Pancytopenia	Bone marrow aspirate and biopsy with cytogenetic testing
Genetic diseases that cause thrombocytopenia (e.g., Bernard–Soulier syndrome and *MYH9*-related disorders)	Young age at presentation, family history of thrombocytopenia, abnormal size and morphologic features of platelets or abnormalities seen in neutrophils on peripheral-blood smear, other clinical abnormalities (e.g., renal disease and deafness in patients with *MYH9*-related disorders)	Peripheral-blood smear, mean platelet volume, genomic testing
Thrombotic thrombocytopenic purpura	Neurologic or cardiac symptoms	Schistocytes on peripheral-blood smear, elevated LDH level, low haptoglobin and ADAMTS13 levels, direct antiglobulin test–negative hemolytic anemia
Heparin-induced thrombocytopenia	Venous thrombosis, previous exposure to heparin	Platelet factor 4–heparin antibody tests, platelet-activation assays
Secondary causes of ITP		
Use of certain drugs	Sudden onset after initiation of new medication (common drugs include quinine or quinidine, acetaminophen, abciximab, carbamazepine, rifampicin, and vancomycin)	Tests to detect drug-dependent antibodies, if available
Lymphoproliferative disorder (e.g., chronic lymphocytic leukemia and Hodgkin's lymphoma)	Weight loss, night sweats, lymphadenopathy or splenomegaly	Complete blood count; peripheral-blood flow cytometry, bone marrow flow cytometry, or both; bone marrow aspirate and biopsy; protein electrophoresis imaging of abdomen, chest, and neck to assess lymphadenopathy and spleen size (as appropriate)
Immunodeficiency syndrome (e.g., common variable immunodeficiency and autoimmune lymphoproliferative syndrome)	Hypogammaglobulinemia, cytopenias, frequent infections (especially chest or sinus infections), colitis, lymphadenopathy, splenomegaly	Immunoglobulin quantification, lymphocyte subset count, genetic testing
Infection (e.g., HIV and AIDS, HBV, HCV, cytomegalovirus, EBV, and *Helicobacter pylori*)	Other suggestive symptoms and signs; at-risk populations	Serologic and PCR tests for HIV, HBV, HCV, cytomegalovirus, and EBV; breath or stool antigen tests for *H. pylori*
Other autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis and antiphospholipid syndrome)	Arthralgias or arthritis, hair loss, sun sensitivity, mouth ulcers, rash, thromboembolism	Tests for antinuclear antibodies, rheumatoid factor, anti–cyclic citrullinated peptide antibodies, antiphospholipid antibodies
Evans syndrome	Thrombocytopenia and direct antiglobulin test–positive hemolytic anemia	Peripheral-blood smear; measurements of haptoglobin and LDH levels; direct antiglobulin test

* ADAMTS13 denotes a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AIDS acquired immunodeficiency syndrome; EBV Epstein–Barr virus; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; LDH lactate dehydrogenase; *MYH9* gene encoding nonmuscle myosin heavy chain 9; and PCR polymerase chain reaction.

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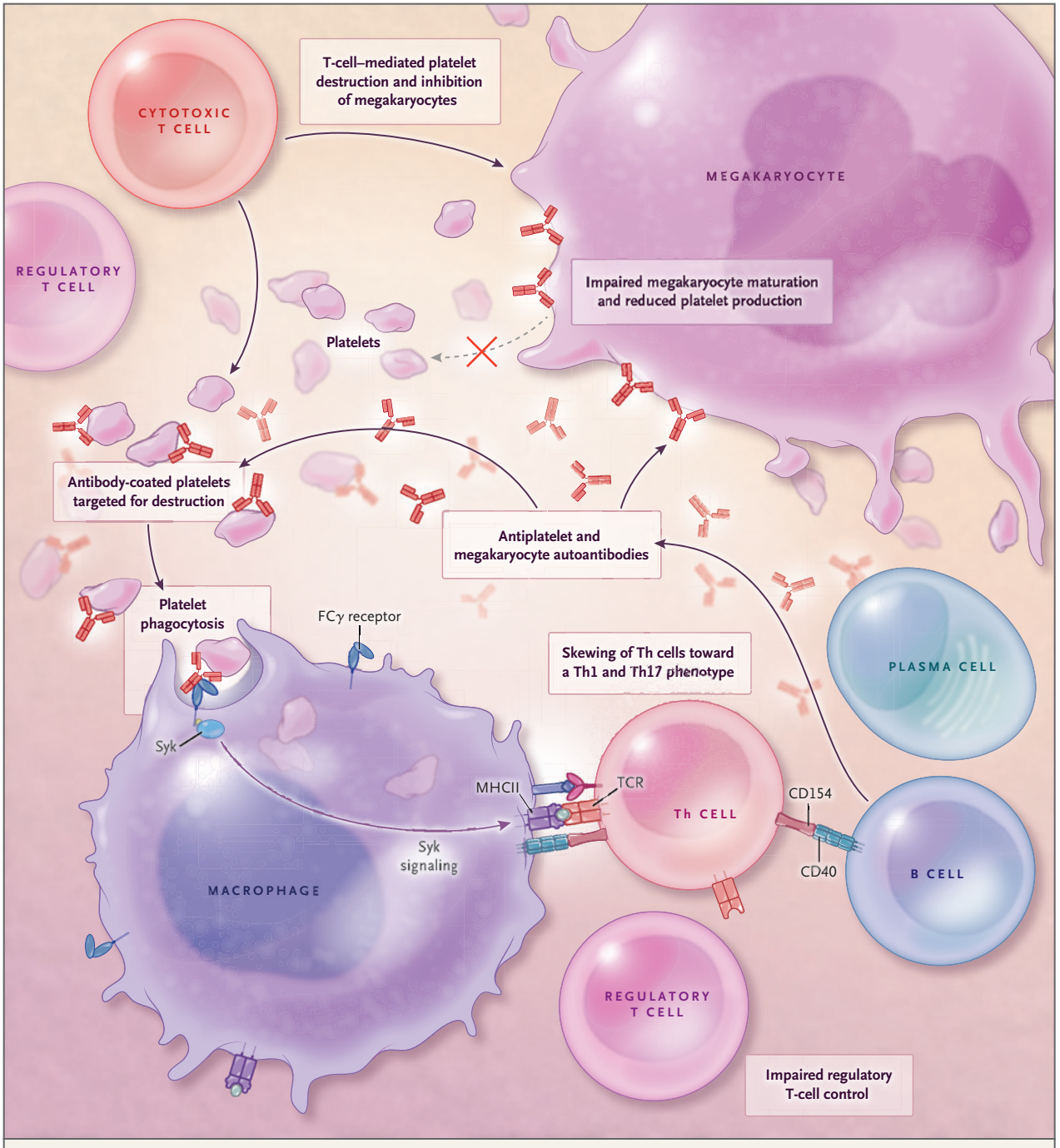

Figure 1. Pathophysiological Features of Immune Thrombocytopenia.

Although the pathophysiology of immune thrombocytopenia (ITP) is incompletely understood, the key event is considered to be the production of antiplatelet autoantibodies. These autoantibodies target platelets for destruction by macrophages in the spleen, liver, or both through activation of Fcγ receptors; this process is controlled by spleen tyrosine kinase (Syk). Autoantibodies may also destroy platelets through other mechanisms and inhibit platelet production by megakaryocytes. Antigens from phagocytosed platelets are thought to be presented by the major histocompatibility complex class II (MHCII) to T-cell receptors (TCRs), stimulating autoreactive T cells. T-cell changes seen in ITP and hypothesized to be pathogenic include skewing of T helper (Th) cells toward a type 1 T helper (Th1) and type 17 T helper (Th17) phenotype, reduction of regulatory T-cell activity, and an increase in cytotoxic T cells. A few studies suggest that cytotoxic T cells can also directly destroy or inhibit the production of platelets.

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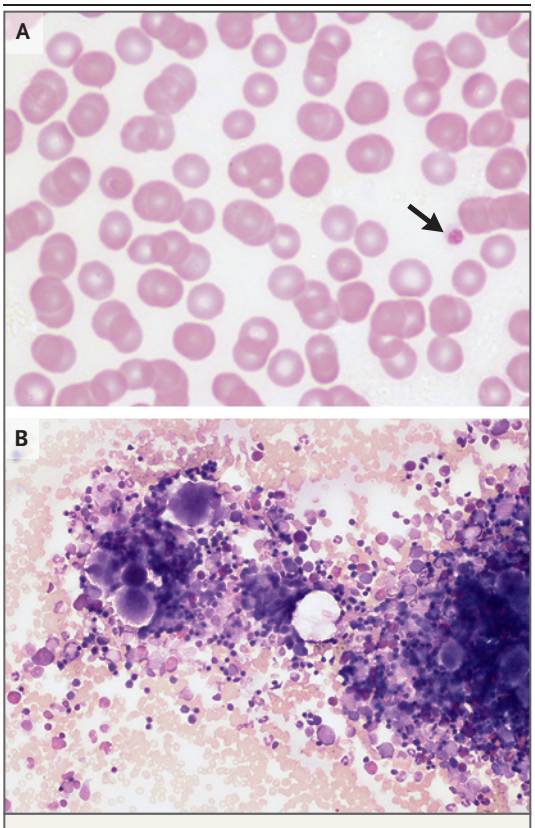

Figure 2. Peripheral-Blood Smear and Bone Marrow Aspirate from a Patient with ITP.

Panel A shows thrombocytopenia (only one platelet [arrow] is observed in the field) and normal erythrocytes in a peripheral-blood smear. Panel B shows bone marrow in a patient with ITP, with good cellularity, normal development of erythroid and myeloid cells, and an increased number of megakaryocytes.

ing, particularly from mucous membranes, and menorrhagia can be treated with hormonal therapy.

Treatment to Prevent Future Bleeding

In patients who are asymptomatic or have only mild mucocutaneous bleeding, the decision to treat should be guided by the risk of future bleeding and patient preferences. However, predicting the risk of future bleeding among patients with ITP is challenging. Several scoring systems have been developed, but their usefulness in clinical practice is limited by their complexity and lack of validation in large studies.[17,19,20]

A platelet count of less than 20,000 to 30,000 per cubic millimeter is frequently used as a criterion for treatment.[16] This criterion is consistent with findings of an increase in the 1-year risk of bleeding requiring hospitalization of 2.5 times among patients with platelet counts between 25,000 and 50,000 and 7 times among those with platelet counts below 25,000 per cubic millimeter.[2] However, treatment decisions should also take into account other risk factors that influence bleeding; these include older age (e.g., >65 years), history of bleeding, concomitant use of anticoagulants and platelet inhibitors, the presence of coexisting conditions such as renal impairment, and the risk of trauma from daily activities.[1,2] It is generally recommended that patients who are receiving anticoagulants or antiplatelet agents should receive treatment to maintain platelet counts above 50,000 per cubic millimeter.

Glucocorticoids

Glucocorticoid treatment is the standard initial therapy for patients with ITP. Two commonly used regimens are pulsed high-dose dexamethasone and a more prolonged course of oral prednisone or prednisolone (Table 2). In a meta-analysis of randomized trials comparing these two regimens, platelet counts were higher at 14 days in patients receiving dexamethasone, but overall responses at 6 months did not differ significantly.[21] Adverse events such as weight gain and cushingoid appearance were more prevalent with prednisone or prednisolone.[21] Other studies have suggested more neuropsychiatric effects with dexamethasone.[15]

Although 60 to 80% of patients with ITP have an initial response to glucocorticoids, only 30 to 50% of adults have a sustained response after glucocorticoids are discontinued.[22,23] In some studies, continued use has been associated with a higher incidence of long-term remission,[24] but prolonged exposure to glucocorticoids is not recommended because of adverse effects.

Other Medical Therapies

Medical therapies for patients with ITP who do not have an initial response to glucocorticoids or who have recurrent decreases in platelet counts after glucocorticoids are discontinued include thrombopoietin-receptor agonists and immunomodulators.[25] In the absence of randomized trials directly comparing these therapies or of biomarkers to guide the choice of medication, treatment

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Table 2. Dosages, Efficacy, and Adverse Effects of Various Treatments for ITP.

Agent	Dosage	Onset of Action	Durability of Effect	Side Effects and Cautions
Glucocorticoids				
Prednisone or prednisolone*	1–2 mg orally for 1–2 wk, followed by gradual tapering; rapid tapering if no response	1–2 wk	Response with treatment in 60 to 80% of patients; sustained response after discontinuation in 30–50% of patients	Weight gain, insomnia, acne, mood changes, cushingoid appearance, glucose intolerance, osteoporosis, increased risk of infection (particularly with prolonged use of prednisone or prednisolone), gastrointestinal symptoms, neuropsychiatric symptoms (particularly with dexamethasone)
Dexamethasone*	20–40 mg orally for 4 days every 2–4 wk; maximum of 4 cycles		Response with treatment in 60 to 80% of patients; sustained response after discontinuation in 30–50% of patients	Weight gain, insomnia, acne, mood changes, cushingoid appearance, glucose intolerance, osteoporosis, increased risk of infection (particularly with prolonged use of prednisone or prednisolone), gastrointestinal symptoms, neuropsychiatric symptoms (particularly with dexamethasone)
Immune globulin*	0.4 g per kilogram of body weight intravenously for up to 5 days or 1 g per kilogram for 1–2 days	1–4 days	Transient response lasting 1–4 wk in ≤80% of patients; treatment can be repeated	Headache, aseptic meningitis, renal failure
Thrombopoietin-receptor agonists†				
Romiplostim*	1–10 μg per kilogram, subcutaneously once weekly	1–2 wk	Response achieved and maintained in 40–60% of patients receiving continuing therapy; response maintained after discontinuation in 10–30% of patients	Headache, muscle aches, possible increased risks of thrombosis and myelofibrosis
Eltrombopag*	25–75 mg orally daily	1–2 wk	Response achieved and maintained in 40–60% of patients receiving continuing therapy; response maintained after discontinuation in 10–30% of patients	Gastrointestinal symptoms, transaminitis, cataract, possible increased risks of thrombosis and myelofibrosis; should be taken 4 hr after and 2 hr before food containing cations (e.g., iron, and calcium from milk or other dairy products)
Avatrombopag*	5–40 mg orally daily	1–2 wk	Response achieved in 65% of patients within 8 days after treatment	Headache, arthralgia, possible increased risk of thrombosis

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Immunomodulators†				
Rituximab	375 mg per square meter of body-surface area intravenously weekly for 4 wk or 1 g administered twice with 2 wk between doses; lower doses (100–200 mg) weekly for 4 wk have also been shown to be effective	1–8 wk	Sustained response in 60% of patients at 6 mo and 30% at 2 yr; treatment can be repeated	Infusion-related side effects (chills, upper respiratory discomfort, bronchospasm), neutropenia, hypogammaglobulinemia, serum sickness; increased risks of infections and progressive multifocal leukoencephalopathy (very rare); should not be used in patients with evidence of active HBV infection (HBV surface antigen) or previous HBV infection (antibodies against hepatitis B core antigen)
Fostamatinib*	50–150 mg orally twice daily	1–2 wk	Response achieved and maintained in 18–43% of patients receiving continuing therapy	Hypertension, nausea, diarrhea, transaminitis
Azathioprine	1–2 mg per kilogram orally (maximum, 150 mg daily)	6–12 wk	Response in 30–60% of patients	Weakness, sweating, neutropenia, transaminitis, increased risk of cancer
Mycophenolate mofetil	500 mg orally twice daily for 2 wk, with gradual increase to 1 g twice daily	4–8 wk	Response in 30–60% of patients	Headache, gastrointestinal symptoms, fungal skin infections, teratogenic in pregnancy, increased risk of cancer
Danazol	400–800 mg orally daily	3–6 mo	Response in 30–60% of patients	Hirsutism, acne, amenorrhea, transaminitis; this androgenic agent should not be used in patients with prostate cancer
Dapsone	75–100 mg orally daily	3 wk	Response in 30–60% of patients	Gastrointestinal symptoms, methemoglobinuria, rash, hemolytic anemia (in patients with glucose-6-phosphate dehydrogenase deficiency)

* This agent is approved by the Food and Drug Administration for use in patients with ITP.
† These agents are used in patients in whom glucocorticoids have failed.

decisions are based on other factors, including the availability of medications, adverse effects, the required speed of response, and patient or physician preference. Among the available options, thrombopoietin-receptor agonists, rituximab, and fostamatinib have undergone the most rigorous study and are addressed below.

Thrombopoietin-Receptor Agonists

Eltrombopag and romiplostim are thrombopoietin-receptor agonists that are approved by the Food and Drug Administration (FDA) for patients with ITP that is refractory to other treatment and with disease lasting more than 6 months (eltrombopag) or 12 months (romiplostim). In randomized, placebo-controlled trials of each of these agents involving patients with chronic ITP in whom at least one previous therapy has failed, 70 to 95% of patients had an increased platelet count with initial treatment and 40 to 60% had durable responses with ongoing treatment.[26,27] Although these agents have not been compared head to head, the incidence of response appears to be similar. A meta-analysis of 13 randomized trials of either agent showed that, as compared with placebo or standard of care, they were associated with significantly higher rates of platelet response and durable response, and they reduced episodes of bleeding and the use of rescue and concurrent medications.[28]

Eltrombopag is administered as a daily tablet (with dietary restrictions), whereas romiplostim is administered in weekly subcutaneous injections (Table 2). The choice between the two agents is guided by the preferred form of administration and anticipated adherence. Limited observational data suggest that if one agent is ineffective, switching to the other results in a platelet response in up to 50% of patients.[29,30]

An initial response to thrombopoietin-receptor agonists usually occurs within 1 to 2 weeks. Once a response is achieved, ongoing treatment is ordinarily required to maintain effect. However, retrospective and prospective cohort studies have shown that 10 to 30% of patients can discontinue treatment after receiving thrombopoietin-receptor agonists for many months or years, and the disease remains in remission, although late relapses may occur.[31,32]

In early studies, concerns were raised regarding possible adverse effects of these agents on bone marrow. However, these effects have not

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been confirmed with more than 10 years of follow-up; moderately increased bone marrow reticulin fibrosis has been observed in fewer than 10% of patients treated with either of these agents and has been reversible on discontinuation.[33] The main safety concern is an increased risk of venous thromboembolism.[4] In extension studies of both agents, thromboembolism developed in 6% of patients during a median follow-up of 2 years.[4,34,35] Thromboembolic events occurred predominantly in patients with other coexisting conditions and risk factors. Although the underlying ITP may partially account for these findings, the incidence of venous thromboembolism in these clinical trials was higher than expected, which raises the possibility that thrombopoietin-receptor agonists may tip the balance to thrombosis in susceptible patients. Other adverse effects of eltrombopag include elevated liver aminotransferase levels (which are reversible when the dose is reduced), and, as shown in animal studies, cataracts (although this finding has not been substantiated in long-term studies involving humans).[34]

Avatrombopag, another oral thrombopoietin-receptor agonist (which, unlike eltrombopag, can be administered without dietary restrictions), was approved by the FDA in June 2019 for the treatment of adults with chronic ITP. This approval was based on results of phase 3 clinical trials showing a longer median number of weeks with platelet counts of 50,000 per cubic millimeter or higher during the first 26 weeks in patients who received avatrombopag than in those who received placebo (12.4 weeks vs. 0 weeks).[36]

Immunomodulators

Rituximab is the most widely used immunomodulator in patients with ITP, although it is not approved by the FDA for this indication. A systematic review of single-group studies showed a response in 60% of patients, with a complete response in 40% of patients.[37] A meta-analysis including five randomized, controlled trials showed a significantly higher incidence of complete response at 6 months with rituximab than with glucocorticoids or placebo.[38] A response to rituximab is typically observed within 1 to 8 weeks (Table 2). In some single-group studies, young women (<50 years of age) with a short duration of disease (<2 years) were reported to have a higher incidence of response and more durable responses than other patients.[39]

The main advantage of rituximab is sustained platelet responses that last more than 2 years in 50% of patients who have a response.[40,41] Although ITP eventually relapses in most patients, most of those in whom the disease relapses have a response to retreatment with rituximab.

An increase in minor infections has been reported with rituximab. However, major complications such as progressive multifocal leukoencephalopathy are exceedingly rare.[41,42]

Fostamatinib, an oral spleen tyrosine kinase (Syk) inhibitor, was approved by the FDA in 2018 for patients with ITP in whom one previous therapy has failed. In pooled randomized trials, a stable response (defined as a platelet count ≥50,000 per cubic millimeter on at least four of six visits twice a week during weeks 14 to 24) was achieved in 18% of patients receiving fostamatinib and in 2% of those receiving placebo. A response (a platelet count ≥50,000 per cubic millimeter within the first 12 weeks of treatment) was achieved in 43% of patients receiving fostamatinib and in 14% of those receiving placebo. The mean time to response was 15 days. Diarrhea, hypertension, transaminitis, and nausea were common adverse effects that occurred in up to 30% of patients.[43]

Other immunomodulatory agents such as mycophenolate mofetil, azathioprine, dapsone, and danazol are also used in patients with ITP (Table 2). Data to support their use are largely limited to retrospective observational studies that suggest that 30 to 60% of patients have a response.[15]

Splenectomy

A systematic review showed that splenectomy, which remains the most effective therapy for ITP, induced long-lasting remissions in 60 to 70% of patients.[44] Nevertheless, owing to the emergence of effective medical therapies, the potential complications of splenectomy, and the inability to predict which patients will have a response,[45] consideration of splenectomy is usually limited to patients who do not have a response to or cannot receive standard medical therapies because of side effects and in whom at least a year has passed since diagnosis (to allow for remission to occur).[46] The frequency of splenectomy has decreased substantially during the past two decades.[47]

Short-term risks of splenectomy include operative and postoperative complications, including

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venous thromboembolism and sepsis. Laparoscopic splenectomy is associated with lower postoperative mortality and morbidity and a shorter recovery time than open splenectomy.[44,48] Although the immediate risk of venous thromboembolism can be reduced by thromboprophylaxis, epidemiologic studies have shown a persistent doubling or quadrupling of the risk of venous thromboembolism among patients with ITP who have undergone splenectomy as compared with those who have not undergone splenectomy.[49,50]

Patients who have undergone splenectomy have an increased risk of infection with encapsulated bacteria and require repeated vaccinations. A large registry-based study showed a higher risk of both early and late sepsis among patients with ITP who had undergone splenectomy than among those who did not.[51]

A higher incidence of other vascular complications, such as coronary artery disease, stroke, and chronic thromboembolic pulmonary hypertension, has also been reported among patients who have undergone splenectomy, but the data are not consistent among studies.[52] Conversely, one study showed no significant difference in mortality in the first year after splenectomy and a lower risk of death after 1 year among patients with ITP who underwent splenectomy than among those who did not.[53]

Splenectomy is generally not performed in frail elderly patients because of increased surgical complications in this group. It is generally not performed in patients with secondary ITP owing to a lower incidence of response and more adverse events in these cohorts than in others.[44,54]

AREAS OF UNCERTAINTY

The pathogenesis of ITP is not fully understood, and biomarkers are needed to predict responses to specific treatments. Randomized trials are lacking to guide the treatment of patients who present with acute serious bleeding and to compare the efficacy and safety of second-line treatments, including with respect to patient-centered outcomes of treatment such as health-related quality of life. Late-stage clinical trials of inhibitors of Bruton's tyrosine kinase (ClinicalTrials.gov number, NCT03395210) and neonatal Fc receptor (NCT02718716 and NCT03102593) are under way.

GUIDELINES

Guidelines for the treatment of patients with ITP were published by an international consensus group[15] in 2010 and by the American Society of Hematology[16] in 2011, but both sets of guidelines antedated many of the studies discussed here and are currently under revision. The American Society of Hematology guidelines recommend splenectomy for most patients in whom glucocorticoids have failed and recommend thrombopoietin-receptor agonists for those in whom splenectomy is contraindicated. Otherwise, there were weak recommendations for the use of rituximab and thrombopoietin-receptor agonists before splenectomy.

Guidelines from a working group of German, Austrian, and Dutch investigators that were published in 2018 recommend thrombopoietin-receptor agonists in patients in whom glucocorticoids have failed and rituximab or splenectomy in those in whom thrombopoietin-receptor agonists have failed.[46] The recommendations in the present article are generally concordant with these more recent guidelines and with the revised guidelines of the American Society of Hematology.[55]

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has a low platelet count without other hematologic abnormalities (with the exception of those accounted for by acute bleeding), consistent with ITP. Urgent treatment to stop the bleeding should include discontinuation of anticoagulation, the use of platelet transfusions, and treatment with IVIG and glucocorticoids. Once her condition has stabilized, her diagnosis should be reviewed, with a careful history to rule out other causes of thrombocytopenia and conditions resulting in secondary ITP. Endoscopic examination is recommended to investigate the source of bleeding.

In the absence of a cure for ITP, the aim in this patient would be to achieve a stable platelet count (usually >50,000 per cubic millimeter) permitting safe reintroduction of anticoagulation. If initial treatment with glucocorticoids and IVIG was not successful in inducing remission or if relapse occurred when glucocorticoids were tapered, we would recommend a thrombo-

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poietin-receptor agonist, given randomized trials showing a high incidence of sustained elevation in the platelet count with each of these agents. However, thrombopoietin-receptor agonists are currently outside the approved indications for ITP, which are limited to ITP lasting for at least 6 months. Rituximab is an alternative therapeutic strategy, although the incidence of response appears to be lower and responses occur more slowly than with thrombopoietin-receptor agonists. Given the patient's age and coexisting conditions, splenectomy would be contraindicated.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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