Immune-mediated thrombocytopenic purpura (ITP) is considered a classical autoimmune disorder characterized as the occurrence of thrombocytopenia (platelet count < 100 × 10^3/mL). Platelet destruction by the spleen and morphologic abnormalities of megakaryocytes followed by their altered matura-
tion are suggested to be the main pathogenic abnormalities in ITP. Later, ITP was well defined to be the result of a plasma factor proven as specific anti-platelet antibodies and finally defining ITP as an autoimmune disorder.¹⁻³ Recent literature accepts the classification of three phases of ITP: (1) the new-onset phase that occurs within 3 months from diagnosis; (2) the persistent phase, lasting between 3 and 12 months from diagnosis; and (3) the chronic phase, defined as lasting more than 12 months.⁴

Patients who are diagnosed with ITP who repetitively bleed considered to have “severe” ITP and they require various therapeutic interventions, including splenectomy and other novel therapies such as rituximab and syk inhibitors.⁵ Though many reports have pointed to the notion that ITP is predominantly a disorder of young women, some have shown a progressive increase in incidence with age. However, the demographics of ITP probably depend on regional differences due to different predisposing infections, and the early diagnosis or the better treatments of B-cell neoplasms.⁶

When ITP is isolated and no evidence for systemic diseases is proven, primary ITP is then defined; primary ITP represents 80% of all cases. However, secondary ITP is defined when various well-proven infectious or autoimmune diseases are responsible for the development of thrombocytopenia. These include viral infections such as hepatitis C virus (HCV), cytomegalovirus (CMV), and Helicobacter pylori, and also cases of ITP that were recognized as a result of vaccination.⁷,⁸ Many viral particles such as HCV were described to polyclonally activate B cells by binding CD81 (part of the B cell co-receptor) or other receptors in the case of CMV, predisposing to the expansion of autoreactive B cells, the production of anti-viral antibodies that cross-react with membrane platelet antigens. In some studies the presence of multiple autoantibodies was documented and suggested to be the result of epitope spreading.⁹,¹⁰ A wide spectrum of autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), antiphospholipid syndrome (APS), and immune deficiencies like common
variable immune deficiency (CVID) are among the list of diseases reported to be responsible for secondary ITP. Chronic lymphocytic leukemia (CLL) and various lymphomas are additional diseases in the list of all the above, all of which do not exceed 20%.11–13

THE DIVERSITY OF IMMUNE-MEDIATED ABERRATIONS IN ITP

Early studies showed already that when isolated platelets from ITP patients were incubated with autologous lymphocytes, they induced their transformation and resulted in increased interleukin (IL)-2 productions. The responsive cells were proven to be CD4⁺ T cells and were shown to react specifically against modified glycoprotein (GP)IIb-IIIa on activated platelets. In addition to CD4⁺ T-cell activation, it was also noticed that the stimulation of ITP B cells resulted in the in vitro production of anti-platelet antibodies. However, the same stimulation of normal B cells did not induce such autoantibodies. Of interest is that the depletion of CD19⁺ B cells was followed by a complete disappearance of these antibodies. Using antigen-specific assays such as immunoprecipitation, immunoblot, and antigen capture techniques, these autoantibodies were shown to be highly specific, and to recognize antigens that are derived from either a single or multiple glycoproteins. The most identified autoantibodies in ITP are those against GPIIb-IIIa and/or GPIb-IX, but there have also been reports of autoantibodies against GPIa-IIa and GPIV.14,15 When assessed positively, these autoantibodies are considered a diagnostic hallmark of ITP with a sensitivity of 49%–66% and a specificity of 78%–93%; however, negative results do not rule out this diagnosis.16 The most likely explanation for negative assays is that other mechanisms are involved in the pathophysiology of ITP that do not involve anti-platelet antibodies, such as T-cell-dependent platelet destruction or inhibition of platelet production.

The persistent destruction of platelets by macrophages induces the continuous processing and presentation of the above membrane glycoproteins by antigen-presenting cells (APCs), which is a crucial step for the generation of pathogenic anti-platelet antibodies. Aiming to better understand this process, GPIIb/GPIIIa-reactive T-cell lines generated from ITP patients were cultured with autologous freshly isolated splenic macrophages, B cells, or dendritic cells (DCs). Macrophages induced the proliferation of GPIIb/GPIIIa-reactive T-cell lines without an exogenous antigen, but B cells and DCs required glycoprotein peptides to stimulate the T cells. Cultured macrophages that captured opsonized platelets promoted anti-GPIIb/GPIIIa antibody production in mixed cultures of autologous GPIIb/GPIIIa-reactive T-cell lines and B cells. The T-cell response was inhibited by anti-FcγRI antibody. Thus, splenic macrophages that take up opsonized platelets via FcγRI are major APCs for cryptic glycoprotein peptides, and are central to the maintenance of anti-platelet autoantibody production in ITP patients.17 In another study, it was reported that macrophages activated by C-reactive protein (CRP) transfer suppression of ITP. Suppression of ITP by CRP-treated splenocytes required FcγRI on the donor cell and FcγRIIb in the recipient mice. These findings suggest that CRP generates suppressive macrophages through FcγRI, which then act through an FcγRIIb-dependent pathway in the recipient to decrease platelet clearance.18

EFFECTOR VERSUS T-REGULATORY CELLS IN ITP

The immune response to glycoproteins in ITP is usually modulated by CD4⁺ effector cells and CD8⁺ cytotoxic cells. In thymus, T cells lose either the CD4 or CD8 antigens and are released as either CD4⁺ effector or CD8⁺ cytotoxic T cells (CTLs). Some self-reactive T cells survive thymic deletion, and persist in peripheral blood as autoreactive and mediate autoimmunity. Normally, autoreactive T cells are controlled by many peripheral self-tolerance mechanisms such as altered co-stimulatory molecules and or failure of T-regulatory (Treg) function. When self-tolerance fails, CD4⁺ T-effector cells react with specific antigens presented by MHCII molecules in association with a proper expression of co-stimulatory molecules. When T cells of ITP patients were stimulated by platelet antigens, one could notice increased production of both Th1 and Th2 cytokines. Th1 cells produce IL-2, interferons, and tumor necrosis factor (TNF), whereas Th2 cells produced IL-4, IL-13, and IL-10, which are considered important in inhibiting cell-mediated immune responses. The role of Th17 (known to be associated with many immune-mediated diseases) in the pathogenesis of chronic ITP was assessed. Higher levels of IL-17A and Th17-related cytokines, and an increased percentage of IL-17A producing CD4⁺ and neutrophils, were observed in ITP patients.19–21 In addition, T-effector cells are increasingly recruited into bone marrow and other involved organs in ITP. To determine the reason for this, expression of chemokine receptors such as CX3CRI and CXCR4 was analyzed in the bone marrow of ITP patients. Here, T-cell surface expression of these chemokine receptors was increased in patients compared with controls. Furthermore, the number of CD3⁺ T cells in bone marrow, but not in blood, along with increased Fas expression was also found, emphasizing the importance of cellular immunity in ITP22 (Figure 1).
T-REGULATORY CELLS

Cellular mechanisms in ITP

Cellular immune-mediated response in ITP is frequently manifested by increased proliferation of cytotoxic T cells. Many studies alluded to the capability of cytotoxic T lymphocytes to alter megakaryocyte development and function, thereby contributing to impaired platelet production. In this respect, cell-mediated lysis of autologous platelets in chronic ITP was observed using purified CD8+ T cells as effector cells. These cells were shown to overexpress Fas-ligand, mRNA levels of granzyme B, perforin, and TNF-α. These results strengthen the concept that apoptosis and perforin/granzyme-mediated cytotoxicity constitute an important pathway through which CTLs destroy autologous platelets (Figure 1).

T-REGULATORY CELLS

The exact mechanisms of autoimmunity in mediating ITP have not been investigated fully, but they definitely include a clear imbalance between the overactivity of effector T cells and the altered function of Tregs. Recent advances in the field of Tregs established their better molecular definition, bringing new insights into their role in maintaining self-tolerance. Therefore it was obvious to assess the role of these cells in ITP. In patients with ITP, naturally occurring CD4+CD25+ Tregs are both functionally impaired and reduced in number. Aiming to establish this finding, Tregs were measured in 44 patients with acute ITP. By using flow cytometry analysis, the number of CD4+CD25+ T cells in patients with ITP showed a very wide distribution in comparison to healthy individuals. The number of Tregs was significantly lower in ITP patients in the severe phase, and in patients positive for anti-GP1b/IIIa antibody. However, the number of those cells increased in patients having full remission, especially after splenectomy. In addition, Foxp3 mRNA levels in peripheral blood mononuclear cells (PBMCs) of ITP patients were higher when patients were in remission than in those with refractory lower platelet counts. In another study, the production and reduced immunosuppressive activity of Tregs in ITP was investigated. The frequency of circulating CD4+CD25+Foxp3+ Tregs in patients and controls was comparable. However, sorted CD4+CD25high cells from patients with chronic ITP (n = 13) had a twofold reduction of in vitro immunosuppressive activity compared with controls (n = 10, P < .05). The impaired suppression was specific to Tregs, as shown by cross-mixing experiments with T cells from controls. These data suggest that functional defects in Tregs are involved in the pathogenesis of ITP. The above findings and others have led to the understanding that the Treg count can possibly correlate with the severity of ITP and, as such, might be used as a tool for diagnosis and assessment of improvement in ITP patients. In spite of their pivotal role in maintaining peripheral immune tolerance, a very small and clinically ineffective number of naturally Tregs (nTregs) can be found in peripheral blood. In their work, Zhang et al demonstrated that platelet GP-specific induced Tregs (GP-iTregs) could be generated de novo from non-regulatory CD4+CD25-CD45RA+ cells in patients with ITP, and induced both antigen-specific and linked suppression. They also showed that the Toll-like receptor pathway is the dominant pathway (along with notch and transforming growth factor-β pathways) related to the GP-specific tolerance.

Aiming to assess the beneficial effect of Tregs in preventing ITP in mice, Treg-deficient mice were studied by inoculation of Treg-depleted CD4+CD25-T cells isolated from BALB/c mice into syngeneic nude mice intravenously. Platelet count, platelet-associated anti-platelet antibodies, and IgG anti-platelet antibody production in splenocyte cultures were examined by flow cytometry. Of 69 Treg-deficient mice, 25 (36%) spontaneously developed thrombocytopenia that lasted at least 5 weeks. The platelet-associated IgG level and proportion of reticulated platelets were elevated in the thrombocytopenic mice. The transfer of Tregs efficiently prevented the onset of thrombocytopenia, but Treg transfer after the onset of thrombocytopenia had no apparent effect. Treatment with IgG anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibodies canceled this Treg-governed suppressive effect. These results indicate that Tregs are capable of
preventing murine autoantibody-mediated thrombocytopenia by engaging CTLA-4 (Figure 1).

**B-CELL AUTOIMMUNITY IN ITP**

Once tolerance for platelet antigens is lost, few pathways can lead to ITP, including antibody-mediated, complement-dependent, and apoptosis. Anti-platelet autoantibodies can bind to platelets and megakaryocytes, where it has been shown to not only cause platelet destruction but also decrease their production by interfering with megakaryocyte maturation/proliferation or by causing intramedullary platelet destruction.30

Autoantibody-mediated complement activation on platelets is a common finding in ITP patients, and its frequency and specificity have been studied. Najaoui et al32 clearly showed that the major targets for complement-fixing autoantibodies are GPIIb/IIIa and GPIb/IX, and that in a significant number of patients with chronic ITP, platelet autoantibodies are capable of activating the classical complement pathway. They reported on the presence of complement fixation even in ITP sera with very low titer of autoantibodies. One of the potential components of autoimmunity in ITP is BAFF (B-cell activating factor of the TNF family), a crucial cytokine for normal development and survival of B cells (Figure 2). In order to investigate this issue, Zhou et al explored the crucial role for BAFF in the pathogenesis of ITP, by measuring BAFF/BAFF-R levels and evaluating the connection between clinical parameters and expression levels.34 They found significantly higher serum BAFF levels in untreated ITP patients compared to normal controls and treated ITP patients. A weak correlation between platelet counts and BAFF levels was noticed. However, no statistical difference in BAFF levels between acute and chronic ITP was found. These results questioned BAFF being a marker for ITP disease activity but clearly point to its role in ITP development and autoimmunity.

Antiphospholipid antibodies (APLA) are frequently found in serum of ITP patients. In their work, Pierrot-Deseilligny et al35 found APLA [anti-cardiolipin (aCL) and/or lupus anticoagulant (LA)] in 26% of 215 ITP patients: anticardiolipin alone in 18%, lupus anticoagulant in 0.5%, and the combination of both in 7%. Thrombotic events, characteristic of antiphospholipid syndrome (APS), were low (7%), but were associated with age and high IgG-aCL levels, suggesting a potential benefit in testing for aPL when ITP is diagnosed. Bidot et al investigated the prevalence of APLA in ITP and APS.36 They observed few differences: (1) IgG and IgM antibodies to β2GP1 were more common in APS than ITP, while IgG antibodies against phospholipids (aCL, anti-phosphatidylcholine, anti-phosphatidylserine, anti-phosphatidylyethanolamine) were more common in ITP than in APS (P < 0.05); (2) multiple APLA (≥ 3 antigens) were more frequent in APS than in ITP (P < 0.05); (3) LA was frequently associated with APS but was absent in ITP; (4) APLA is quite common in ITP—two-thirds of subjects were positive for at least one APLA. They concluded that the APLA profile differs between ITP and APS. In APS, antibodies were mainly against β2GP1 and 80% had positive LA, while in ITP the APLA react mostly with the phospholipids without LA. These differences might explain the opposite clinical presentations in the two diseases: thrombotic versus bleeding. Pratt et al described the prevalence of antithyrold antibodies (ATA) and antinuclear antibodies (ANA) in children with ITP. Twenty-three percent of children with acute ITP had acute non-platelet antibodies detected. In the chronic ITP patients group, 33% had at least one abnormal antibody value (ATA, ANA). Most of the patients testing positive for autoantibodies were female and/or 12 years of age or older. Their results suggest patients with acute ITP who also have other autoantibodies may be more likely to develop chronic ITP than those lacking these autoantibodies.37

**THE DEVELOPMENT OF SLE IN ITP PATIENTS**

The issue of ITP being primary or secondary to SLE was the subject of many studies. When secondary, ITP is usually mild to moderate, and the

![Humoral mechanisms in ITP](image-url)

**Figure 2.** Humoral mechanisms in ITP: anti-platelet antibodies: (A). GPlib/IIa are presented to Th1 effector cells. These enhance the proliferation of autoreactive B cells and the production of anti-GPlib/IIa antibodies. (B) Autoreactive B cells are stimulated by increased levels of BAFF. This is followed by a continuous production of anti-platelet antibodies. (C) Anti-GPlib/IIa bind megakaryocytes and inhibit their maturation to normal platelets.
treatment in this case is different, especially when ITP is present in association with other hematologic findings. Anti-platelet antibodies were reported to be detected in 78% of SLE patients, often without concurrent thrombocytopenia, and in up to 16% of patients, isolated thrombocytopenia was their initial clinical manifestation. The early recognition of patients in whom isolated ITP is likely to progress to SLE is crucial due to its both prognostic and therapeutic importance.\textsuperscript{38–40}

Several studies have attempted to identify clinical or laboratory parameters that could possibly predict which of the ITP patients are likely to develop SLE or other autoimmune diseases. In this respect, Anderson and co-authors found that 24 of 117 adult patients with ITP (20%) had a positive ANA titer. Four of these patients developed later SLE; all of them were women with high titers of ANA.\textsuperscript{41} In a smaller study, six of 18 adult women with ITP (33%) and positive ANA developed SLE within 4 years, all with high ANA titer (\(\geq 1:160\)).\textsuperscript{42} In another study, 16 of 82 adult patients with chronic ITP (20%) had a positive ANA recorded. Nine of these patients developed SLE within 6 months of ITP onset.\textsuperscript{43} These data suggest that high titers of ANA in women with ITP are a sensitive but nonspecific marker for predicting the development of SLE. However, one should point to other contrary experiences among children with chronic ITP and ANA positivity who remained free of any evidence of autoimmune diseases. With this point of view, Kurata et al reported on 29 adult patients with chronic ITP and positive ANA, but none of whom developed SLE during a 3-year follow-up period.\textsuperscript{44}

In order to further clarify this issue, the clinical significance of ANA positivity in children with chronic ITP was further studied. To do so, a long-term follow-up study of a large cohort was performed to determine the likelihood that selected children with ITP will develop signs and symptoms of systemic autoimmune disease.\textsuperscript{45} Here, 147 children with ITP were enrolled and divided by sex into boys (n = 77) and girls (n = 70) and to those defined as having acute (n = 69) or chronic (n = 78) ITP. The average age of these patients was 7.0 \pm 4.8 years. ANA was assessed in only 87 of these patients, typically at the time of diagnosis as a screening test or due to an additional symptoms or a positive family history. ANA was found to be positive (a median titer of 1:160) in 25 of the 87 tested children. Correlations between ANA results, family history of autoimmune diseases, initial hemoglobin concentration, initial platelet count, and/or the finding of elevated platelet autoantibodies were not evident during a short follow-up. However, when long-term follow-up were examined, a higher incidence of autoimmune symptoms was noted in the group of children with positive ANAs. Of the 25 children with positive ANAs, nine (36%) had further autoimmune symptoms during the follow-up period as compared to none in the 62 children with negative ANAs (\(P < .001\)). These were predominantly girls (n = 8) with a mean age of 12.2 years at diagnosis and most of them had chronic ITP (n = 7) rather than acute. Autoimmune symptoms were more frequent in those with ANA titers \(\geq 1:640\) than those with lower titers (67\% vs 31\%), although this difference was not statistically significant (\(P = .20\)). Moreover, children with a positive ANA together with other autoantibodies, such as anti-dsDNA, were significantly more likely to develop further autoimmune symptoms (57\% vs 0\%, \(P = .04\)). The author’s conclusion was that, similar to the experience noted by many in adults, the presence of a positive ANA (especially of high titers) together with the presence of other autoantibodies, especially those to dsDNA, can be helpful in identifying those patients with ITP who are at increased risk of develop SLE. Several other reports demonstrated later that female patients with chronic ITP, high titers of ANA, and additional autoantibodies (such as anti-dsDNA, cardiolipin, anti-SSB-La/SSA-Ro) are candidates for developing SLE in the future.\textsuperscript{46–48} Therefore, physicians have to look for a combination of autoantibodies such as anti-dsDNA, cardiolipin, and anti-Ro/La, specific medical and familial history, and physical examination in order to better identify the minority of cases in which the ITP heralds future SLE.

**NOVEL THERAPIES FOR ITP**

The decision for treatment in patients with ITP must take into account several factors, including the age of the patient, the severity of the illness, and the anticipated natural history. Adult patients, particularly those older than 60 years of age, have a higher incidence of major or fatal bleeding than children.\textsuperscript{49} However, therapy may not be necessary unless the platelet count is \(< 20 \times 10^9/L\) or when extensive bleeding develops. This review focuses on recent advances in ITP treatment and not on traditional approaches. The main goal of second-line therapy is to attain a continual increase of the platelet count, which is considered hemostatic for the patient. The following treatment modalities have quite different mechanisms of action, but they are intended to induce long-term remission.

**Rituximab-Specific Anti-CD20 Antibody**

Rituximab was found to be highly useful in ITP patients, where 60\% of them are usually considered responders, with 40\% achieving complete response. Responses generally occur between 2–8 weeks of
rituximab as a second-line treatment for chronic ITP. Initial complete response and prolonged B-cell depletion are considered useful predictors for sustained responses. In a prospective study, follow- ing one treatment of rituximab, 33% of patients had a platelet count of $50 \times 10^9$/L or higher and 40% had a platelet count of $30 \times 10^9$/L or higher. In this respect, most patients with a durable (>1 year) complete response will respond to a repeated treatment when they relapse. In the above studies, rituximab was used in doses of 375 mg/m², but lower doses (100 mg administered intravenously weekly for 4 weeks) also may be effective, although associated with a longer time to response. Further studies are warranted to identify the optimal dose and the best treatment protocol. Recently it has been reported that high response rates were shown for a combination of rituximab with high-dose dexamethasone as initial therapy. At this stage, one should question whether rituximab could be a better treatment choice than splenectomy in order to achieve remission as a second-line therapy. Although having fewer side effects, there are not enough current data to support the replacement of splenectomy with rituximab as a second-line treatment for chronic ITP.

The main mechanisms by which rituximab is beneficial in patients with ITP is by eliminating normal B cells, but also those producing anti-platelet antibodies. This B-cell depletion is almost always transient and has few side effects or toxicities. Rituximab was shown also to exert significant effects on cellular immunity. Pretreatment abnormalities of T cells in ITP patients were reverted in responders of rituximab as opposed to non-responders, where they remained unchanged. By being immunomodulatory, rituximab produces clinical remission in ITP when expansion of pathogenic T cells is still dependent on B-cell costimulation. However, when ITP is advanced and T-lymphocyte clones are more expanded, they continue to drive B-cell activity and antibody production, irrespective of the cytokine microenvironment produced in turn by these B cells. A large clinical trial supported the notion that at this stage of ITP rituximab is ineffective. In this study, patients with a short duration of disease, in whom presumably T-cell expansion was B-cell-dependent, were much more likely to respond to treatment than those with longer ITP duration. Therefore, non-responsiveness to anti-CD20 therapy in ITP may be related to an inability to modify the oligoclonal nature of the T-cell subsets.

Adverse effects of rituximab are usually mild or moderate, with a low incidence of infections. There are also reports of several cases with progressive multifocal leukoencephalopathy associated with rituximab treatment in patients with lymphoma and and patients with SLE and ITP, who were heavily immunosuppressed and on combination treatments. Thus, additional long-term safety data are required.

Thrombopoietin-Receptor Agonists: Romiplostim and Eltrombopag

Until now, all known treatments for ITP were generated in order to suppress the production of autoantibodies and/or inhibiting macrophage-mediated destruction of opsonized platelets. However, some ITP patients have impaired platelet production rather than increased platelet destruction. Additionally, ITP patients have normal or slightly elevated thrombopoietin (TPO; the main regulator of platelet production) levels. These levels are lower than the serum levels found in patients with megakaryocytic hypoplasia, probably as a result of active TPO uptake and destruction by the expanded megakaryocyte mass in ITP. With this in mind, the uses of TPO for stimulation of megakaryopoiesis and the increase of platelet count in ITP were suggested. The first-generation of TPO used in clinical trials included recombinant human TPO (rhTPO), and a non-glycosylated, truncated form of TPO coupled to polyethylene glycol. The recombinant protein, called “megakaryocyte growth and differentiation factor” (MGDF), had structural and immunogenic differences compared to native TPO, due to which immunogenic adverse effects were noticed. Clinical trials were discontinued after the development of TPO autoantibodies was demonstrated in healthy volunteers and did not yield a clinically therapeutic advantage. Recently, intense research and development has been focused on second-generation thrombopoietic growth factors. These new molecules have no structural resemblance to TPO, but still bind and activate the TPO receptor, and were hence given the name of “TPO-receptor agonists.” Studies have been completed and the US Food and Drug Administration approved two TPO mimetics, romiplostim and eltrombopag. Romiplostim is administered as a 1-10 mg/kg subcutaneous weekly injection. Eltrombopag is an oral non-peptide TPO-receptor agonist administered as a 25, 50, or 75 mg daily dose. Data from clinical trials have demonstrated that both drugs are highly effective in increasing the platelet count in both healthy volunteers and ITP patients. In two placebo-controlled, double-blind randomized trials, romiplostim was given to splenectomized and non-splenectomized ITP patients for 6 months. An overall platelet response rate (>4 weeks out of 24 study weeks $> 50 \times 10^9$/L) was observed in 79% and 88% of romiplostim-treated patients, compared with 0% and 14% in the respective placebo treatment
group. In these romiplostim studies, it was demonstrated that 87% of romiplostim-treated patients had reduced or discontinued other modalities of ITP therapy, including corticosteroids and intravenous immunoglobulin. Long-term follow-up of patients treated with romiplostim showed that responses were sustained for 4 years on continuous therapy and that most ITP patients were able to decrease or even discontinue concurrent corticosteroid therapy. This is an important therapy result, since many of these patients are on immunosuppressive treatment for a long period of time.

Similar results have been demonstrated with eltrombopag in chronic relapsed or refractory ITP patients. Although most adverse effects were mild, the main concern of these therapies is the increased bone reticulin, which was found in 10 of 271 patients included in the romiplostim trials and in seven of 117 patients in the eltrombopag trials (<6% overall). Further studies are warranted in order to determine the importance of this finding. Another side effect was liver function test abnormalities, which were seen in 13% of eltrombopag-treated patients. Due to their mechanism of action, these TPO-receptor agonists are considered as a maintenance therapy. Upon cessation of treatment, most patients return to lower platelet counts (>10% transiently falling below baseline platelet counts); however, few patients are able to discontinue treatment successfully.

CONCLUSION

Both humoral and cellular mechanisms are involved in the development of ITP. The role of Tregs is of special pathogenic importance and could be applied in future therapeutic approaches. Patients in whom ANA, aPL, and anti-dsDNA antibodies exist are candidates to develop SLE and or APS. New novel therapeutic approaches are already in practice for refractory ITP patients.

REFERENCES


