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Immune Thrombocytopenia: Recent Advances in Pathogenesis and Treatments

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Abstract

Immune thrombocytopenia (ITP) is a rare autoimmune disease due to both a peripheral destruction of platelets and an inappropriate bone marrow production. Although the primary triggering factors of ITP remain unknown, a loss of immune tolerance—mostly represented by a regulatory T-cell defect—allows T follicular helper cells to stimulate autoreactive splenic B cells that differentiate into antiplatelet antibody-producing plasma cells. Glycoprotein IIb/IIIa is the main target of antiplatelet antibodies leading to platelet phagocytosis by splenic macrophages, through interactions with Fc gamma receptors (FcγRs) and complement receptors. This allows macrophages to activate autoreactive T cells by their antigen-presenting functions. Moreover, the activation of the classical complement pathway participates to platelet opsonization and also to their destruction by complement-dependent cytotoxicity. Platelet destruction is also mediated by a FcγR-independent pathway, involving platelet desialylation that favors their binding to the Ashwell-Morell receptor and their clearance in the liver. Cytotoxic T cells also contribute to ITP pathogenesis by mediating cytotoxicity against megakaryocytes and peripheral platelets. The deficient megakaryopoiesis resulting from both the humoral and the cytotoxic immune responses is sustained by inappropriate levels of thrombopoietin, the major growth factor of megakaryocytes. The better understanding of ITP pathogenesis has provided important therapeutic advances. B cell-targeting therapies and thrombopoietin-receptor agonists (TPO-RAs) have been used for years. New emerging therapeutic strategies that inhibit FcγR signaling, the neonatal Fc receptor or the classical complement pathway, will deeply modify the management of ITP in the near future.

Generality and triggering factors of immune thrombocytopenia

Immune thrombocytopenia (ITP) is a rare autoimmune disease with an incidence around 3/100,000 person-years, with a peak among males older than 75 years (9/100,000 person-years). Factors initiating ITP are unknown, but seasonal fluctuations have been observed with an increased incidence during winter, suggesting a role for viral infections.[1] However, both persistent and chronic ITP (>3 mo, and >12 mo after diagnosis, respectively) affect 70% of adult patients and are less prone to such fluctuations, suggesting the involvement of other factors. Although genetic predispositions such as major histocompatibility complex (MHC) subtypes, cytokine or cytokine receptor polymorphisms, have been reported as favoring factors of ITP or involved in its maintenance, none appears relevant in clinical practice.[2] Innate lymphoid cells (ILC) could participate in the initiation of the autoimmune process as supported by the expansion of splenic ILC1 that produce the proinflammatory cytokines interleukin (IL)-2 and interferon (IFN)-γ.[3]

ITP is referred to as secondary—that is, associated to another disease—in 20% of cases, mostly hematological malignancies, followed by systemic autoimmune diseases such as lupus, infections, and primary immune deficiencies.[4] Among infections, Epstein-Barr virus, cytomegalovirus, hepatitis C virus (HCV), and HIV are the most documented,[2] with recent reports of severe acute respiratory syndrome coronavirus 2-associated ITP.[5] These associations are partly due to a molecular mimicry between platelet glycoprotein (GP) IIIa and HIV GP120 or HCV core envelope 1 protein.

Overall, 80% of ITP are considered as primary, favored by a rupture of the immune tolerance leading to an autoimmune process involving both innate and adaptive immune responses.

Peripheral destruction of platelets

An integrative view of ITP pathogenesis is summarized in Figure 1 and Table 1.

Humoral response and antiplatelet antibodies

The involvement of the humoral response against platelets is known since the 1950s when Harrington et al[6] observed that sera of ITP patients induced thrombocytopenia when infused to healthy volunteers. It was further shown that IgG

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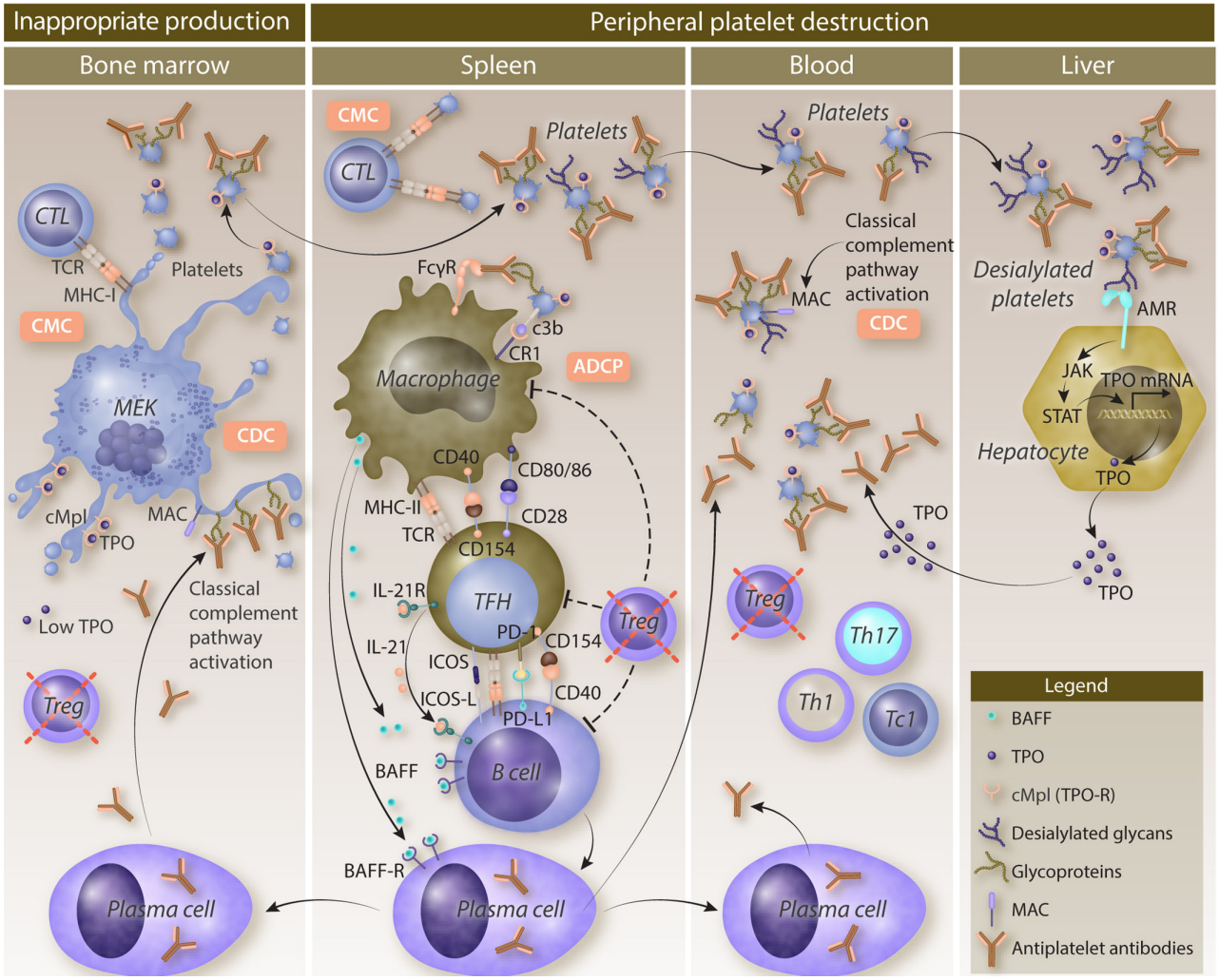


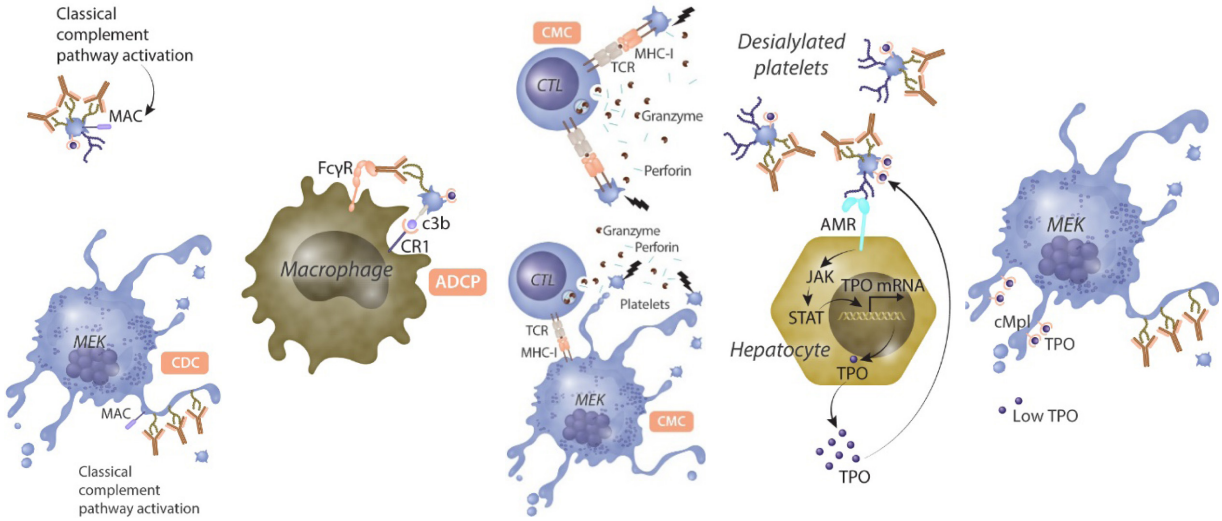
Figure 1. ITP pathogenesis. ITP results from a peripheral destruction of platelets that takes place in the blood, the spleen, and the liver, together with an inappropriate bone marrow production due to an autoimmune response against megakaryocytes and insufficient TPO levels. In the blood, platelet destruction is most probably mediated by CDC: the binding of antibodies to platelet GP leads to the activation of the classical complement pathway and the formation of the MAC, leading to platelet lysis. Complement activation also leads to the deposition of C3b on platelet surface, which promotes the phagocytosis of opsonized platelets by macrophages in the spleen, mediated by the ligation of antiplatelet antibodies to FcγR and C3b to CR1. Splenic macrophages are the major antigen-presenting cells that stimulate autoreactive CD4 T cells in ITP. These autoreactive T cells contain TFH cells that interact with autoreactive B cells and induce their proliferation, their differentiation into plasma cells, and the production of antiplatelet antibodies by a mechanism dependent on IL-21 secretion and CD40/CD154 interactions. BAFF is a cytokine produced by monocytes (and polymorphonuclear cells) that participates to the stimulation and survival of B cells and plasma cells. Antiplatelet antibodies, by the recruitment of neuraminidase-1 at platelet membrane, trigger platelet desialylation. Desialylated platelets are recognized by the Ashwell-Morell receptor expressed on hepatocytes, leading to their removal from circulation and to the production of TPO, the major growth factor of megakaryocytes. In the bone marrow there is an autoimmune response against megakaryocytes that express similar GP as platelets and are thus recognized by antiplatelet antibodies and exposed to CDC and ADCP. Of note, bone marrow also represents a niche for autoreactive plasma cells. CD8 cytotoxic T cells can mediate cytotoxicity against platelets; however, due to the necessity of a close cell contact, this phenomenon probably takes place in the spleen rather than in the blood. Moreover, there is a recruitment of CTL into the bone marrow where they participate to the immune response against megakaryocytes. Overall, the autoimmune response is favored by a loss of tolerance, supported by a deficiency of Tregs in the spleen, the blood and the bone marrow. ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; AMR = Ashwell-Morell receptor; BAFF = B-cell activating factor; CD = cluster of differentiation; CDC = complement-dependent cytotoxicity; CMC = cytotoxic T lymphocyte-mediated cytotoxicity; cMpl = thrombopoietin receptor; CR = complement receptor; CTL = cytotoxic T cell; FcγR = Fc gamma receptor; GP = glycoprotein; ICOS = inducible T-cell costimulator; ICOS-L = ICOS ligand; IL = interleukin; ITP = immune thrombocytopenia; JAK = janus kinase; MAC = membrane attack complex; MEK = megakaryocyte; MHC = major histocompatibility complex; mRNA = messenger RNA; PD-1 = programmed cell death protein 1 (CD279); PD-L1 = programmed cell death ligand 1 (CD274); STAT = signal transducer and activator of transcription; Tc = cytotoxic T cell; TCR = T-cell receptor; TFH = T follicular helper cell; Th = helper T cell; TPO = thrombopoietin; Treg = regulatory T cell.

were responsible for this effect by targeting various platelet GPs, notably GPIIb/IIIa (fibrinogen receptor), GPIb/IX (von Willebrand factor) and less frequently GPIa/IIa (collagen receptor) and GPIV.[7,8] In clinical practice, direct monoclonal antibody immobilization of platelet antigens assay (MAIPA) allows the detection of antiplatelet antibodies in up to 85% of ITP patients, against GPIIb/IIIa in 66.7% of the cases, GPIb/IX in 60% of the cases, GPIa/IIa in 40.6% of the cases, and GPIV in 26.9% of the cases.[8] Anti-GPV antibodies have recently been detected in ITP patients: they were associated with anti-GPIb/IX in most of the cases, and were the unique antiplatelet antibody detected in only 2.9% of the patients.[9] Despite their lower avidity to platelets, their involvement in platelet destruction has been confirmed in a murine model.[9]

The spleen plays a major role in ITP pathogenesis, being the site of an intense autoimmune response with an expansion of germinal centers and the generation of mutated, high-affinity-antiplatelet antibody-secreting plasma cells.[10] Some of these

Table 1

Mechanisms Leading to Thrombocytopenia During ITP.

Mechanisms	CDC	ADCP	T-Cell Mediated Cytotoxicity	Platelet Desialylation	Inappropriate Thrombopoietin Concentration
Actors	Antiplatelet antibodies (anti-GPIIb/IIIa > anti-GPIb/IX) Classical complement pathway (MAC formation)	Antiplatelet antibodies/FcγR Classical pathway activation (C3b deposition)/CR Macrophages	CD8 T cells	Antiplatelet antibodies (anti-GPIb/IX > anti-GPIIb/IIIa?) Ashwell-Morell receptor on hepatocytes	Thrombopoietin/hepatocytes
Targets	Platelets Megakaryocytes	Platelets (Megakaryocytes?)	Platelets Megakaryocytes	Platelets	Megakaryocytes
Site of actions	Blood Spleen Bone marrow	Spleen (Bone marrow)	Spleen Bone marrow	Liver	Bone marrow
Schema					

ADCP = antibody-dependent cellular phagocytosis; AMR = Ashwell-Morell receptor; CD = cluster of differentiation; CDC = complement-dependent cytotoxicity; CMC = cytotoxic T lymphocytes-mediated cytotoxicity; cMpl = thrombopoietin receptor; CR = complement receptor; CTL = cytotoxic T cell; FcγR = Fc gamma receptor; GP = glycoprotein; ITP = immune thrombocytopenia; JAK = janus kinase; MAC = membrane attack complex; MEK = megakaryocyte; MHC = major histocompatibility complex; mRNA = messenger RNA; STAT = signal transducer and activator of transcription; TCR = T cell receptor; TPO = thrombopoietin.

plasma cells migrate to the bone marrow where they can reside as long-lived plasma cells.[11] Although IgM antiplatelet antibodies have been observed,[12,13] most antibodies are IgG, notably IgG1 (77% of the cases)[14] harboring somatic hypermutation in variable immunoglobulin genes.[15] Splenic T follicular helper cells (TFHs) participate in the selection of autoreactive B-cell clones in germinal centers.[16]

Various mechanisms support the cytotoxicity mediated by antibodies, such as complement-dependent cytotoxicity (CDC), causing the destruction of targeted cells by the formation of the membrane attack complex (MAC),[17,18] but also facilitating their phagocytosis (antibody-dependent cellular phagocytosis [ADCP]) by macrophages expressing Fc gamma receptor (FcγR) and complement receptor 1 that binds to the complement fraction C3b.[19] Another mechanism, antibody-dependent cellular cytotoxicity (ADCC) mediated by natural killer (NK) cells, is probably less involved during ITP.[20]

The involvement of complement was investigated in the 1980s[19] and is currently of particular interest as complement inhibitors have reached clinical development. An activation of the classical complement pathway by the sera of ITP patients is observed in 50%–60% of the cases, as assessed by complement deposition on platelets.[18,21] This activation correlates with the presence and the type of antiplatelet antibodies, ranging from 33% when not detected, to 81% when detected in the sera; anti-GPIIb/IIIa antibodies being more prone to activate complement pathways than anti-GPIb/IX (73%–100% versus 40%–65%).[18] The increase in soluble MAC during the active phase of ITP, the inverse correlation of its levels with platelet numbers, and its positive correlation with the presence of antiplatelet antibodies also attest to CDC involvement.[22] Moreover, classical complement pathway activation is associated with a decrease in circulating immature platelets, a platelet fraction that reflects bone marrow production, thus arguing for a CDC also mediated against megakaryocytes that disrupts platelet production.[21,23]

ADCC mediated by NK cells has been scarcely studied in ITP. Although, the frequency of circulating NK cells is comparable to the ones of controls, their cytotoxic activity tended to be higher in the spleen during ITP.[20] However, another study reported that NK cells were not capable of platelet lysis, contrary to cluster of differentiation (CD) 8 T cells.[24]

A major mechanism of peripheral platelet destruction is ADCP, mediated by splenic macrophages. Recently confirmed in humans, the phagocytosis involved the ligation of opsonized platelets to FcγRI and FcγRIII, but not FcγRII.[25] Combined to their phagocytic functions, splenic macrophages also endorse the role of major antigen-presenting cells (APCs) in ITP. Indeed, ex vivo isolated splenic macrophages of ITP patients highly stimulate the proliferation of anti-GPIIb/IIIa T-cell clones, as compared to dendritic cells and B cells that require prior antigen loading.[26] Consistent with these APC functions, splenic macrophages highly express MHC class II and the costimulatory molecule CD86 during ITP.[27]

Contrary to anti-GPIIb/IIIa antibodies, it has been suggested that anti-GPIb/IX contributes to platelet destruction by an FcγR-independent pathway due to platelet desialylation, a mechanism involved in their physiological regulation.[28] During their life span, platelets progressively undergo desialylation, that is,

the loss of sialic acid of their membrane glycans, leading to the exposition of galactose that is recognized by the Ashwell-Morell receptor (AMR), an hetero-oligomeric receptor (asialoglycoprotein receptors 1 and 2) expressed by hepatocytes.[29,30] The binding of desialylated platelets to AMR leads to their removal from the circulation and the activation of a janus kinase 2/signal transducer activator of transcription 3 transduction pathway inducing the production of thrombopoietin (TPO), the main growth factor of megakaryocytes.[30] In a mouse model of ITP, anti-GPIb/IX antibodies trigger platelet desialylation by the translocation to the platelet membrane of neuraminidase-1, a sialidase, thus favoring their destruction in a FcγR-independent pathway, while platelet destruction by anti-GPIIb/IIIa antibodies requires FcγR.[28] Supporting this mechanism, oseltamivir, an inhibitor of neuraminidase-1, reduces thrombocytopenia in this model.[28] Whether these different mechanisms are relevant in clinical practice remains controversial. Considering these 2 different potential pathways of platelet destruction, it was suggested that intravenous immunoglobulines (IVIG), whose effects are partly dependent on FcγR, could be less efficient in patients with anti-GPIb/IX compared to those with anti-GPIIb/IIIa.[31] A study conducted on 156 ITP patients treated with IVIG showed a response in 36.4% (24/66) of patients with anti-GPIb/IX antibodies compared to 80% (72/90) of patients without these antibodies.[32] In a smaller cohort of 69 patients, these results were not confirmed, probably due to the fact that anti-GPIb/IX antibodies were rarely isolated and that these different mechanisms of platelet destruction could be intricated at a patient level.[33] Similarly, considering this potentially specific mechanism of action of anti-GPIb/IX antibodies, it has been assumed that platelet destruction should predominantly occur in the liver of these patients, which was not confirmed by isotopic platelet scintigraphy.[34] Likewise, an increase in TPO level was also expected in presence of anti-GPIb/IX antibodies, which was not confirmed in a recent study showing similar levels of TPO whatever the type of antiplatelet antibodies.[35]

Conversely, the use of oseltamivir in 241 flu-infected patients and 102 noninfected controls showed a significant increase in platelet count (around 55×10^9/L by mean) when compared to 42 flu-infected patients not receiving oseltamivir (increase by 18×10^9/L by mean).[36] Another study involving 35 ITP patients showed that the level of platelet desialylation was greater in multirefractory patients who were nonresponders to steroids, and TPO-RAs used in all cases, and to IVIG, immunosuppressants, rituximab, or splenectomy used in 81.3%, 68.8%, 62.5%, and 37.5%, respectively.[37] Compared to nonrefractory patients, the frequency of isolated anti-GPIb/IX antibodies tended to be higher (31% versus 10.5%).[37] Interestingly, 10 multirefractory patients were treated with oseltamivir: used as monotherapy, no response was observed, while to be suppressed achieved in 66.6% when combined to TPO-RA or immunosuppressant, despite previous unresponsiveness.

These results highlight that other factors than anti-GPIb/IX antibodies participate to the desialylation of platelets. The main pitfall is that the first demonstrations were obtained from mouse models and that in humans, such a dichotomy between the mechanisms of action of anti-GPIb/IX and anti-GPIIb/IIIa is probably not present. Indeed, sera containing anti-GPIIb/IIIa antibodies also cause the platelet desialylation in humans, by a mechanism requiring a cross-linking to platelet FcγRIIA,[38] that is not expressed by mice. Adding to the complexity, antibody-mediated desialylation can affect megakaryocytes and reduces the formation of proplatelets, this impairment being reversed by sialidase.[38]

Overall, desialylation appears to be involved in both platelet destruction and production and is associated with a lower platelet count and a refractoriness to usual therapies.[31,37,38] Whether sialidase inhibitors could be of interest as an add-on therapy remains to be confirmed.

T-cell immune dysregulation

The role of CD4 T cells in ITP has been known for years, with clones recognizing GPIIb/IIIa detected in the spleen and the blood of ITP patients in the early 2000s.[39,40] Interestingly, the frequency of circulating clones diminishes after splenectomy in responder patients, highlighting their involvement in the autoimmune process and the fact they may reside in places other than the spleen.[40]

Similarly to most of autoimmune diseases, an imbalance between the proinflammatory and the anti-inflammatory responses is present during ITP, with a skewing of T cells to helper T cell (Th) 1[41] and Th17[42] polarizations, associated with a quantitative[43] or functional[44] deficiency of regulatory T cells (Treg). This Treg deficiency participates to the maintenance of the autoimmune process in multiple sites during ITP, such as the blood,[45] the spleen,[46] and the bone marrow.[47] Interestingly, Treg deficiency improves in response to dexamethasone,[48] rituximab,[44] or TPO-RA.[49] Similarly, the response to rituximab is associated with a reversal of the Th1 polarization.[44]

TFH are expanded within splenic germinal centers where they stimulate B cells to differentiate into plasma cells and to produce antiplatelet antibodies by a mechanism requiring the interaction between CD40, expressed by B cells, and CD154 expressed by TFH and the secretion of IL-21 by TFH.[16] We also observed that the presence of TFH in the spleen depends on B cells, as TFH were no longer detected in the spleen of ITP patients treated with rituximab.[50] In mice, the maintenance of TFH phenotype requires a sustained antigenic stimulation and interactions with germinal center B cells, through inducible T-cell costimulator (ICOS)/ICOS ligand and CD40/CD154.[51] Otherwise, TFH downregulate the expression of their canonical transcription factor B-cell lymphoma 6, and the membrane markers C-X-C chemokine receptor 5 and programmed cell death protein 1 (PD-1).[52] Thus, it cannot be excluded that after rituximab treatment, memory TFH with a modified phenotype still reside in the spleen, and that after B-cell reconstitution, they recover their usual phenotype and functions and stimulate autoreactive B cells. Such a mechanism could be involved in the relapse of ITP following initial response to rituximab in some patients.

The role of cytotoxic T lymphocytes (CTL) in ITP was shown in the early 2000s by their capability to lyse platelets,[24] associated with increased plasma concentrations of the cytotoxic proteins granzyme A and B.[53] However, the main issue is the capability of CTL to target a sufficient number of platelets to trigger thrombocytopenia, as close contact is required for CTL cytotoxicity and the CTL:platelet ratio is 1:100 to 1:400 in the blood. Thus, CTL cytotoxicity could take place in the spleen, whose architecture could favor close contact between cells. We observed an increase in IFN-γ secreting CD8 T cells (cytotoxic T cell), with a memory phenotype and expressing granzyme B in patients who were nonresponders to rituximab, suggesting a T cell-mediated rather than a B cell-mediated disease in these patients.[54]

Besides peripheral destruction of platelets, CTL cytotoxicity also affects megakaryocytes, as supported by their higher recruitment in the bone marrow, driven by fractalkine, a chemokine that binds to CX3CR1 expressed by CTL,[47] and their capability to interfere with the platelet production.[55]

Inappropriate platelet bone marrow production

Combined to the peripheral destruction of platelets, there is an inappropriate production in ITP resulting from both an immune response against megakaryocytes but also to inadequate level of TPO.

As megakaryocytes express different GP recognized by antiplatelet antibodies, they are exposed to the humoral immune response that diminishes their number and maturation,[56] and to the CTL cytotoxicity that disrupts physiological apoptotic mechanisms involved in platelet formation.[47,55]

During ITP, the inappropriate levels of TPO are linked to its physiological regulation. The production of TPO by hepatocytes is stimulated by the recognition of senescent desialylated platelets by the AMR. TPO activates megakaryocytes by binding to TPO receptor (cMpl), that is also expressed by platelets. Thus, the pool of circulating platelets directly participates to their regulation: in case of thrombocytopenia, the amount of free TPO reaching megakaryocytes is high, thus stimulating platelet production, while in case of thrombocytosis, great amounts of TPO bind to platelets, leaving only small quantities of free TPO to stimulate megakaryocytes.[57] During ITP, the pool of platelets reaching circulation is close to what is normally observed, allowing the binding of high amounts of TPO to platelets that are rapidly destroyed, thus leading to thrombocytopenia by a shortening of their lifespan. This results in a lower concentrations of TPO in ITP patients compared to patients suffering from aplastic anemia with similar platelet counts.[58]

This insufficient platelet production supports the use of TPO-RA, whose efficacy inversely correlates with endogen TPO concentrations.[59]

Therapeutic targets in ITP

The current treatments of ITP, together with new therapeutic classes recently licensed or under investigation, are summarized in Table 2. They have recently been reviewed and detailed elsewhere.[60]

Current management of ITP

First-line therapy relies on corticosteroids that are effective in a few days in 85% of cases, but with a frequent relapse after discontinuation. As neither prednisone/prednisolone nor dexamethasone modify the course of ITP, their long-term use is not recommended.[61] Corticosteroids' effects are mediated by a wide inhibition of the immune response, affecting B cells, T cells, macrophages, and dendritic cells. The mechanisms responsible for the nonresponse to steroids, observed in 10%–15% of ITP patients, are still undetermined.

IVIG exert their immunomodulatory functions by various mechanisms that are not completely elucidated. Notably, the Fc portion of IVIG favors the clearance of autoantibodies by saturating the neonatal Fc receptor (FcRn) and inhibits IgG activating receptors (CD16/FcγRIII, CD32A/FcγRIIA, CD64/FcγRI).[62] The increased expression of the inhibitory receptor CD32B/FcγRIIB by IVIG remains controversial as it has been demonstrated in

Table 2

Targets and Mechanisms of Action of Different Classes of Drugs Currently Used or of Potential Interest (in Italic) for the Management of ITP.

Targets	Drug Classes	Mechanisms of Action
B cells and plasma cells		General mechanism: decrease in antiplatelet antibody production, thus reducing ADCP, CDC and ADCC
	Steroids	Immune cell inhibition (B and T lymphocytes, macrophages, dendritic cells)
	Immunosuppressants	Immune cell inhibition (B and T lymphocytes, macrophages, dendritic cells)
	Splenectomy	Removal of autoreactive splenic B cells and plasma cells
	Anti-CD20	B-cell depletion, notably short-lived plasma cell precursors
	Anti-CD19	B cell and plasma cell depletion
	Anti-CD38	B cell and plasma cell depletion
	Proteasome inhibitors	Plasma cell inhibition and apoptosis
	Anti-BAFF	Combined with anti-CD20, reduces the formation of long-lived plasma cells
Antiplatelet antibodies	*FcRn blockers*	Increase in antiplatelet antibody clearance
Classical complement pathway	*C1s inhibitors*	Decrease in CDC
		Decrease in platelet opsonization by C3b, thus decreasing ADCP (not firmly demonstrated)
Macrophages	Steroids	Decrease in ADCP and modulation of APC functions
	IVIG	Decrease in ADCP (inhibition of activating FcγR)
	Splenectomy	Removal of the site of destruction of platelets and of autoimmune response
	Vinca-alkaloids	Inhibition of cytoskeleton proteins thus inhibiting ADCP
	Recombinant Ig multimers	Decrease in ADCP (inhibition of activating FcγR)
	Syk inhibitors	Decrease in ADCP (inhibition of FcγR transduction signal)
	BTK inhibitors	Decrease in ADCP (inhibition of FcγR transduction signal)
Effector T cells	Steroids	T-cell inhibition
	Immunosuppressants	T-cell inhibition
	Splenectomy	Removal of the site of TFH and B-cell interactions
	Anti-CD154	Disruption of activation pathway btw T cells and APC, TFH and B cells
	Anti-CD40	Disruption of activation pathway btw T cells and APC, TFH and B cells
	Anti-IL-21	Inhibition of activation of B cells by TFH
Regulatory T cells	*Low dose IL-2*	Restoration of Treg function
Megakaryocytes	TPO-RAs	Increase in platelet production by megakaryocytes
	rhTPO	Increase in platelet production by megakaryocytes
Platelets	*Neuraminidase inhibition*	Decrease in platelet desialylation thus reducing their destruction in the liver

ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; APCs = antigen-presenting cells; BAFF = B-cell activating factor; BTK = Bruton tyrosine kinase; CD = cluster of differentiation; CDC = complement-dependent cytotoxicity; FcRn = neonatal Fc receptor; FcγR = Fc gamma receptor; Ig = immunoglobulin; IL = interleukin; ITP = immune thrombocytopenia; rhTPO = recombinant human thrombopoietin; Syk = spleen tyrosine kinase; TFH = T follicular helper cell; TPO = thrombopoietin; TPO-RAs = thrombopoietin-receptor agonists; Treg = regulatory T cells.

animals[63] but not confirmed on circulating monocytes[64] nor splenic macrophages in humans.[27] Unresponsiveness to IVIG accounts for 10%–20% of ITP patients[65] and could be due to a preferential involvement of CTL in platelet destruction, as shown in a mouse model.[66]

Due to the central place of B cells in ITP pathogenesis, rituximab has been proposed for many years, with response rates of 40%, and 30% at 1- and 5-year follow-up.[67] By depleting B cells, anti-CD20-targeting therapies diminish antiplatelet antibodies[68] via reducing the formation of autoreactive plasma cells. However, nonresponse to rituximab is observed in around 40% of the cases. This can be due to the persistence of long-lived splenic plasma cells that did not express CD20[10] and whose survival is maintained by a microenvironment enriched in the cytokine B-cell activating factor (BAFF).[69] Another mechanism may be the preferential involvement of CTL in platelet destruction, as supported by the increase in splenic effector memory CTL with a clonal restriction in nonresponders to rituximab.[54]

Despite response rates to rituximab that are higher in patients with anti-GPIIb/IIIa antibodies (75%) compared to those without (46%),[70] the determination of antiplatelet antibodies cannot be considered as a reliable marker to decide for or against the use of rituximab at a patient scale. To date, there is no valuable predictive factors of response to rituximab in clinical practice.

TPO-RA increase platelet production by megakaryocytes and have been used in ITP for more than 10 years, with response rates of 60%–90%.[71–74] First considered as merely a suspensive therapy, long-term remissions after transient use of TPO-RA are observed in around 15% of cases.[75,76] This raised the possibility of immunomodulatory properties that need to be fully deciphered and could partly rely on a restoration of Treg functions.[49]

Despite a long-term response achieved in 66% of the cases, the use of splenectomy has declined over time, mostly due to the availability of multiple efficient medications.[77] Moreover, splenectomy is associated with increased risk of infections, particularly in the quarter following surgery, while the long-term risk is similar to the one of nonsplenectomized ITP patients.[77,78] After splenectomy, there is also an increased risk of venous thromboembolism,[79] while arterial events are as frequent as for nonsplenectomized ITP patients.[79,80]

The efficacy of splenectomy is based on the removal of the site of platelet destruction and of maintenance of the autoimmune process.[10,16] Unresponsiveness to splenectomy has been attributed to various causes such as the destruction of platelets in the liver or the bone marrow, as shown by platelet scintigraphy,[81] or the persistence of autoreactive plasma cells in other niches such as the bone marrow.[11] To date, there is no formal predictive factor of response to splenectomy, although platelet scintigraphy can be useful, since an exclusive splenic clearance of platelets is associated with a response in 87% of the cases, compared to 47% and 25% in case of mixed or hepatic destructions.[82]

Future therapeutic perspectives

Phagocytosis inhibition

As the phagocytosis of platelets by macrophages relies on FcγR, drugs interfering with its transduction signal have been developed. Among the multiple molecules engaged in this process, spleen tyrosine kinase (Syk) was first targeted. Syk is recruited by the phosphorylation of intracellular activating motives (immunoreceptor tyrosine-based activation motif) of the intracellular domain of FcγR, and participates to the phosphorylation cascade resulting in the activation of phagocytosis and the production of cytokines.[83] Fostamatinib is a Syk inhibitor approved in ITP by the US Food and Drug Administration, based on the results of clinical trials showing a response rate around 43% in previously heavily treated patients, with a prolonged response in 18% of patients.[84] Sides effects are mostly represented by diarrhea in 31% of patients, and hypertension in 28% of patients; this latter effect being due to interferences with vascular endothelial growth factor receptor signaling in endothelial cells.[85] This highlights the need for a long-term follow-up to assess the potential effects on vascular remodeling by long-term inhibition of Syk.

The Bruton tyrosine kinase (BTK) is another molecule implicated in FcγR signaling. One issue of BTK inhibition is the disturbance of platelet aggregation, as BTK is also expressed by platelets. This has led to the engineering of rilzabrutinib, a modified BTK inhibitor not affecting platelet aggregation. It showed promising results in a phase I/II study, with a good safety profile and a response achieved in 44% of 32 chronic ITP patients and maintained in 71% of weekly counts.[86]

Of note, both Syk and BTK contribute to B-cell receptor signaling and could possibly affect antibody production.

Inhibition of the neonatal receptor of the Fc portion of immunoglobulins (FcRn)

The FcRn has a major role in prolonging the lifespan of both IgG and albumin.[87] FcRn is expressed by endothelial cells of various organs and binds to IgG and albumin within acidified endosomes, redirecting them to blood circulation, while unbounded proteins are degraded in lysosomes.[87] FcRn inhibitors have been developed, such as the monoclonal antibodies rozanolixizumab[88] and nipocalimab,[89] or efgartigimod—a modified Fc portion of IgG_1.[90] Phase I/II studies have shown a good tolerance and a response in 38% of ITP patients for efgartigimod[91] and 50% for rozanolixizumab.[92] As expected, a decrease in IgG concentrations was observed, while IgA or IgM concentrations were not affected. More surprisingly, albumin concentration remained stable.[88,90]

Modulation of phagocytosis by recombinant multimeric immunoglobulins

Although IVIG are highly efficient in ITP, their availability depends on blood donations, leading to recurrent transient shortages. To avoid such an issue, recombinant multimeric immunoglobulins are being developed.[93]

B cell- and plasma cell-targeting therapies

Anti-CD20 monoclonal antibodies (veltuzumab, obinutuzumab) have been humanized to limit the induction of antidrug antibodies. Despite its good tolerance and efficiency, veltuzumab is not routinely used in clinical practice.[94] Obinutuzumab has also been engineered to increase its cytotoxicity and B-cell depletion in hematological B-cell malignancies. Whether this amelioration is of interest in ITP to increase response rates or response duration has not yet been investigated.

The nonresponse to rituximab, partly due to the emergence of long-lived plasma cells in a BAFF-enriched microenvironment,[10] raised the interest of a combination of rituximab with belimumab, a monoclonal therapy targeting BAFF. First assessed in a murine model of ITP, this combination therapy showed a dramatic decrease in splenic plasma cells.[69] These promising results were confirmed in a clinical trial with a response achieved in 80% of the 15 ITP patients receiving this combination therapy, as compared to historical response rates of 40%–50% to rituximab monotherapy.[95,96]

Another way to deplete long-lived plasma cells is the use of proteasome inhibitors, such as bortezomib, licensed in multiple myeloma; this could be useful to deplete autoreactive plasma cells in ITP.[97] Similarly, monoclonal antibodies directed

against clusters of differentiation expressed by plasma cells such as CD38 or CD19 could be interesting. Daratumumab, an anti-CD38 therapy, has shown its efficiency in a case study of a patient with a postallogenic transplantation ITP, who was not responding to rituximab.[98] Anti-CD19 antibodies are under investigation in other antibody-mediated diseases (neuromyelitis optica spectrum disorders, myasthenia gravis, IgG_4-related disease).[99] However, the major issue of plasma cell depletion is the risk of profound hypogammaglobulinemia that could favor infectious complications and preclude their routine use.

T cell-targeting therapies

As a key costimulatory molecule expressed on dendritic cells and TFH, the inhibition of CD154 has been investigated. However, anti-CD154 led to low response rates in ITP (16%–43%)[100] and all clinical trials were suspended because of thrombosis reports due to platelet activation by the engagement of CD154 (CD40L) expressed on their membrane. To avoid thrombosis issues, new anti-CD154 therapies with either a modified Fc portion or lacking the Fc portion, involved in platelet activation, are being developed.[101,102] Anti-CD40 antibodies are also of interest by their capability to inhibit the development of germinal centers, B-cell activation, and the production of antibodies in animal models.[103]

Considering the mechanism of action of TFH in the stimulation of B cells, the blockade of IL-21 is a relevant field of investigation.[104]

Besides the inhibition of autoreactive T cells, the restoration of the immunosuppressive functions of Treg or their expansion could be an alternative. In line with this, low dose of IL-2, tested in patients with various autoimmune diseases, showed an increase by 25% of circulating activated Treg without expanding effector T cells.[105] The study is ongoing to determine the clinical relevance of this strategy.

Interestingly, chidamide, a histone deacetylase, increases the immunosuppressive functions of Treg and convert effector T cells into Tregs in vitro, leading to the improvement of ITP in a murine model,[106] thus highlighting the potential interest of epigenetic modulation in ITP.

Inhibition of the classical complement pathway

The clinical evaluation of sutimlimab, a C1s inhibitor, has exhibited the capability to revert classical in vitro complement pathway activation.[17] The primary results of a phase I study conducted on 12 ITP patients showed a response within the 24 hours following infusion in 42% of the cases, a complete response in 33% of the cases, a prolonged response in 42% of the cases, and no safety issues, indicating the potential interest of this new therapeutic strategy in ITP.[107]

Inhibition of platelet desialylation

Considering that platelet destruction is partly supported by platelet desialylation and their clearance in the liver, oseltamivir, a neuraminidase-1 inhibitor, has been occasionally used in refractory ITP. It showed its potential by improving response to immunosuppressants or TPO-RA in 10 out of 16 multirefractory ITP patients with anti-GPIb/IX antibodies.[37] Further prospective studies are needed to determine its potential value in clinical practice.

Enhancement of thrombopoiesis

With similar mechanisms of action than eltrombopag, but without dietary interactions, the TPO-RAs avatrombopag and lusutrombopag have exhibited safety and efficiency.[108,109] While avatrombopag is licensed in ITP,[108] lusutrombopag is indicated for chronic liver disease-related thrombocytopenia.[109] Of note, a human recombinant TPO is used in China, with a response rate of 60% in ITP,[110] without development of anti-TPO antibodies and the advantage of not being contra-indicated during pregnancy.

Conclusions

The advances in the deciphering of ITP pathogenesis support the view of ITP as a syndrome rather than a unique pathology. Different pathological pathways lead to a common feature—thrombocytopenia—and are probably involved at different levels at a patient scale, as supported by the highly variable responses to drugs with different mechanisms of action from a patient to another. New molecules with original mechanisms of action will soon be available in ITP, expanding the crucial need for biomarkers to help clinicians tailoring treatments to patients.

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