Recent advances in the mechanisms and treatment of immune thrombocytopenia

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Summary

Primary immune thrombocytopenia is an autoimmune disease associated with a reduced peripheral blood platelet count. The phenotype is variable with some patients suffering no bleeding whilst others have severe bleeding which may be fatal. Variability in clinical behaviour and treatment responses reflects its complex underlying pathophysiology. Historically the management has relied heavily on immune suppression. Recent studies have shown that the older empirical immune suppressants fail to alter the natural history of the disease and are associated with a poor quality of life for patients. Newer treatments, such as the thrombopoietin receptor agonists, have transformed ITP care. They have high efficacy, are well tolerated and improve patients’ quality of life. A greater understanding of the underlying pathophysiology of this disorder has helped develop a number of new targeted therapies. These include inhibitors of the neonatal Fc receptor inhibitors, Bruton tyrosine kinase and complement pathway. Here we discuss the mechanisms underlying ITP and the new approach to ITP care.

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Introduction

Autoimmune disease places a significant burden on the healthcare system affecting between 3-9% of the population.¹ According to the British Society of Immunology, £13bn is spent on treating autoimmune diseases in the UK (www.immology.org). Despite advances in management, the morbidity and mortality remain high for many of these disorders.

Primary immune thrombocytopenia is an organ-specific autoimmune disease characterised by a reduced peripheral blood platelet count.² Symptoms and signs include fatigue in addition to dry or wet purpura. Many patients have few or only mild symptoms but severe and life-threatening bleeding may occur. Somewhat frustratingly, even today, ITP remains a diagnosis of exclusion; there should be no detectable underlying cause for the thrombocytopenia found on investigation.¹

ITP in which there is a detectable underlying cause is termed secondary ITP but we will not discuss this here. The reduced peripheral blood platelet count is a result of a combination of premature platelet destruction and a relative inadequacy of platelet production.³ In addition to antibody-mediated platelet destruction, which has been recognised since the 1950s,⁴ other mechanisms are clearly involved. These include T-cell mediated apoptosis of megakaryocytes, inhibition of platelet production and T cell destruction of platelets.⁵ The underlying pathophysiology is better understood today and has led to the development of new treatments including the TPO-RA, syk inhibitor, Fcy receptor (FcγR) inhibition, and other treatments.

ITP Pathophysiology

It has been 70 years since the famous Harrington-Hollingsworth experiment was performed showing that plasma from patients with ITP caused significant thrombocytopenia when infused into healthy volunteers.⁶⁻⁷ It now appears that B and T cell defects are a central feature of ITP pathophysiology (Figure 1) and the most compelling evidence is that platelet autoimmunity is caused by a failure of self-tolerance mechanisms.⁸⁻¹⁰ A summary of these mechanisms will be discussed.
Defects in antigen presenting cells
Essentially all IgG responses, including autoimmune IgG production in ITP, are initiated by T helper cells that recognize their cognate peptide antigens in association with major histocompatibility complexes (MHC) on antigen presenting cells (APC). APC are a diverse set of cells which include dendritic cells (DC), macrophages and in some instances, B cells. Recent studies have suggested that even platelets and their parental cells, the megakaryocytes, can act as antigen presenting cells. DCs are the most potent professional APC within the innate immune system and many reports have demonstrated their impairment in ITP. For instance, Catani et al. demonstrated that DCs had the ability to stimulate autoreactive T cell proliferation upon platelet challenge in vitro and this was attributed to elevated CD86 expression on the DC surface. Furthermore, low numbers of plasmacytoid DCs (pDCs) were observed in patients with primary ITP and those affected by secondary ITP associated with Helicobacter pylori infection, and these low numbers significantly correlated with low platelet counts. It was suggested that a lack of type I interferon secreted by the pDCs may play a role modulating activated autoreactive T cells in ITP. Perhaps more important were the observations of Catani et al. who showed that DC-associated indoleamine 2,3-dioxygenase 1 (IDO1) was reduced in patients with ITP and this was thought to impair the differentiation of regulatory T cells (Tregs) which contributes to the observed Treg deficiency in ITP (Figure 2). As DC are the most efficient of all APC populations, it is not surprising that their abnormalities play an important role in ITP T cell pathogenic mechanisms, and molecules directed at correcting DC defects may be an attractive avenue for ITP therapy. With regards to macrophages, it is well known that they are the primary phagocyte responsible for splenic platelet destruction in ITP. In addition, these cells, particularly during states of inflammation e.g. bacterial infections, can be activated by inflammatory cytokines such as IFN-γ to up-regulate MHC class II molecules and enhance the antigen presenting capability of the cells. This may lead to a double edge sword in ITP where the macrophage not only destroy autoantibody-opsonized platelets, but also processes and present platelet autoantigens to autoreactive T helper cells. Such a scenario may contribute a continuous autoantigen feedback loop, which needs to be broken by immunosuppressive therapy.

Soluble factors
Patients with ITP also have numerous abnormalities associated with soluble immune mediators such as cytokines/chemokines and complement proteins. In the early 1970s, one of the first observations of cytokine impairment in ITP was the excessive in vitro production of macrophage inhibition factor (MIF) by lymphocytes from patients with ITP. This pioneering study may have been one of the first descriptions of a T cell abnormality in ITP as MIF is primarily a T cell-derived factor, although other cell types have now been shown to harbour this preformed cytokine. Subsequently, many publications of other cytokine abnormalities have been reported which have culminated in the broadly accepted...
dogma that active ITP is a manifestation of Th1 and Th17 cytokines most probably due to a lack of Treg suppression of autoimmunity.9,10,23,24 The inverse relationship between Th1/Th17 cytokines and lowered Treg activity in ITP is striking and, of interest, the common factor associated with reversing this relationship is the increase in platelet counts (mass) in patients after treatment with a wide variety of different therapies.25 This is not a surprising finding as platelets contain high amounts of transforming growth factor (TGF)-β, a major molecular switch to induce Treg production.26-31

With respect to complement, the IgG autoantibodies formed in ITP have the ability to fix complement and complement components are found on the platelet surface.32,33 Both these processes can contribute to platelet destruction in ITP. Despite these observations, little research has been performed on serum complement in ITP and limited data exist on whether complement levels play a significant role in disease pathophysiology. In spite of this, however, therapeutics targeting complement such as the C1 esterase inhibitor sutimlimab are currently being studied in the treatment of ITP.34,35

**NK & T lymphocyte dysregulation**

Natural killer (NK) cells are a cytotoxic lymphocyte of the innate immune system that have rapid responses against virally-infected host cells and are activated by tumour formation.36,37 They have a unique ability to recognize and kill target cells in the absence of antibodies and/or MHC expression which allows them to act quickly on abnormal cells. Early studies suggested that although NK cell numbers in the peripheral blood of patients with ITP were relatively normal, their ability to kill K562 erythroleukaemic target cells in vitro was significantly suppressed.38 Subsequently, Ebbo et al39 demonstrated that NK cytotoxicity was also suppressed in spleen cells from patients with ITP. More recently, El-Rashedi et al40 examined NK cells in children with ITP and concluded that childhood ITP is associated with an increase in cytotoxic T lymphocytes, but a decrease in peripheral blood NK cells. The reasons for these observations are unclear, particularly since patients with ITP have elevated levels of interferon-γ which is predominantly produced by NK cells.24,41 However, NK cells are known inhibitors of B cell differentiation and affinity maturation42,43 and thus, it may be that their suppressed activity can influence autoantibody production in ITP (Figure 2).

Perhaps the first paper to suggest that autoantibody production in patients with ITP is not autonomous, but under the control of T cell regulation, was proposed by Hymes et al.44 This early study suggested that a defective CD8+ T cell suppression was responsible for the excessive production of anti-platelet autoantibodies. It then took almost 27 years for the notion that lack of T cell suppression was apparent in ITP when Liu et al45 demonstrated that patients with ITP have defective and reduced numbers of CD4+ T regulatory cells. Thus began an impressive output of papers all showing defective Tregs in ITP and this laid the foundation that ITP is due to a lack of peripheral T cell tolerance mechanisms.5,9

**Figure 2.** Potential mechanisms of self-tolerance breakdown in ITP. Dendritic cell abnormalities may play a central role in inhibiting Treg and Breg suppressive activities while stimulating autoreactive effector mechanisms (Figure 1). In addition, defects in NK cells and MDSCs may also contribute to autoimmune generation.
Review

Other defects in cells involved in immune responses
In addition to Treg abnormalities in ITP, several other myeloid and lymphoid abnormalities have been documented that probably also play a role in the pathogenesis of the disorder. For example, Li et al. elegantly demonstrated that CD19+CD24+CD38+ B regulatory cells (Bregs) are reduced in number and defective in ITP, characterized by deficient production of the anti-inflammatory cytokine IL-10. This leads to the inhibition of monocyte TNF-α expression, but more intriguingly, when thrombopoietin (TPO) therapy increased platelet counts in the patients with ITP, it also increased Breg numbers and function, just as observations showing increases in platelet counts following TPO therapy rescues the Treg deficiency in ITP (Figure 2). Thus, the compromised Breg compartment causes significant immune dysregulation in ITP and like Tregs, this cell population may be an efficacious target for therapy. Alternatively, in contrast to the low numbers of Breg in the periphery, Aslam et al. found Bregs to be significantly elevated in the spleens of patients with ITP suggesting that peripheral reductions of Breg numbers, at least, may be due to sequestration of these potent immunoregulatory cells. On the other hand, myeloid-derived suppressor cells (MDSCs) have also been shown to be abnormal in patients with ITP. MDSCs are a heterogeneous population of myeloid progenitor cells that have been shown to be potent regulators of adaptive immunity having the ability to inhibit T cell proliferation by starving the cells of nutrients required. Hou et al. demonstrated that MSDC were deficient in patients with active ITP and that high dose dexamethasone treatment rescued the MSDC numbers and restored Treg function (Figure 2). This work suggests a necessary role for MDSC in the pathogenesis and corticosteroid management of ITP and analogous results with respect to MSDC numbers were observed in spleen cell cultures from ITP patients treated with intravenous immunoglobulin (IVIg).

Given the wealth of information now known about the pathophysiology of ITP, there are several potential immune mechanisms that may be targeted by therapy. In particular, active ITP is the result of a lack of immune tolerance due to faulty Tregs and any therapeutic design to elevate Tregs will ultimately raise platelet counts in patients. These aspects are summarized in Figure 2. It is clear, however, that more basic and clinical research is required to unfold the precise mechanisms responsible for immune dysregulation in ITP.

Treatment goals for ITP
The goals of ITP management have not been clearly defined although the most recent International Consensus Report attempts to better define these. The primary focus of management is the prevention of bleeding and patient safety by elevating the patient’s platelet count up to 20-30 × 10⁹/L. The goal of “safety” rather than normalization of the platelet count was outlined many years ago by Karpatkin. Until quite recently there were few formally approved treatments for ITP. The most common treatment modality that has been used in ITP is immune suppression. This has been achieved using corticosteroids, immune suppressants such as azathioprine, mycophenolate, cyclosporin A, and rituximab, in addition to chemotherapy agents, the attenuated androgen danazol, and dapsone, an antibacterial. These drugs are of variable efficacy, often accompanied by significant unwanted effects and their benefits to the patients are questionable. Patients may feel more unwell with the treatment than from the disease itself.

We will discuss the new era of ITP therapy here, beginning with the second generation thrombopoietin receptor agonists (TPO-RAs), before examining the recent ITP therapy, fostamatinib. A number of other agents are in clinical development including neonatal Fc receptor inhibitors, Bruton tyrosine kinase inhibitors, and anti-complement drugs.

Table 1 summarises the recent treatments designed for primary ITP.

Models of treatment
Many of the treatments used in autoimmune disease achieve few lasting remissions. The focus for many autoimmune diseases has shifted towards improving symptoms and health-related quality of life. The same is true for ITP where quality of life has been recognised as a major treatment goal for this disease.

The treatment models in current medical practice include: the infectious disease model, oncologic disease model, metabolic disease model, and transplant rejection model. Over many decades, ITP has been managed using the transplant rejection model in which suppression of the immune system has been used to ameliorate the disease symptoms. It is clear from many published studies, and the recent I-WISH study, that this model seldom induces remissions and has serious adverse effects on morbidity or mortality, resulting in an overall poor quality of life for patients with ITP. Given that ITP is a “benign” disorder, it is disappointing that treatments offer few benefits to patients whilst, at the same time, badly affecting their health-related quality of life.

Shift in emphasis away from immune suppression
Over the past few years there has been a gradual shift away from immune suppression as a means of treating ITP. The recent COVID-19 pandemic has made immune suppression very unattractive as a modality of treatment since our focus has been on minimising patient risk from COVID. The TPO-RAs have filled this gap and in England and Wales, as well as other territories (Interim Clinical Commissioning Policy, NHS
Thrombopoietin (TPO) mimetic agents

In order to move away from immune suppression, the first-generation TPO-mimetic drugs were developed in the 1990s including recombinant human TPO (rHu-TPO) and recombinant human megakaryocyte growth and development factor (rHu-MGDF). By stimulating the TPO receptor these agents raised the patients’ platelet counts. However, although these TPO mimetics had good efficacy in ITP, antibodies were generated against the drugs in some patients.65 However, although there were fewer treatment failures in the mycophenolate arm, the quality-of-life was lower in this group. For this reason, in addition to the avoidance of immune suppression during the current pandemic, few patients have actually received mycophenolate upfront.

Table 1: Recent treatments designed for primary ITP.

| Drug                        | Description | Mechanism of action |
|-----------------------------|-------------|---------------------|
| Romiplostim60–71             | Peptibody TPO-RA | Stimulates the JAK-STAT pathway. Megakaryocyte proliferation, maturation and platelet production |
| Eltrombopag61,71             | Small molecule TPO-RA | Stimulates the JAK-STAT pathway. Megakaryocyte proliferation, maturation and platelet production |
| Avatrombopag74              | Small molecule TPO-RA | Stimulates the JAK-STAT pathway. Megakaryocyte proliferation, maturation and platelet production |
| Fostamatinib61,62           | Syk inhibitor | Decreases antibody-dependent phagocytosis of platelets |
| Efgartimomod63              | Anti-FcRn    | Decreases the half-life of IgG, reduces plasma IgG both normal and pathogenic |
| Rozanolixizumab70           | Anti-FcRn    | Decreases the half-life of IgG, reduces plasma IgG both normal and pathogenic |
| Rituximab68,69              | BTKI         | Inhibits Fcγ signal transduction, decreases platelet phagocytosis and autoantibody production |
| Suitimlimab64               | Anti-C1s     | Decreases complement-dependent cytotoxicity thereby reducing platelet destruction |

Inhibition of FcγR platelet destruction: syk inhibition

Another novel agent for ITP is fostamatinib, a small molecule syk inhibitor. This oral agent acts by inhibiting syk and prevents platelet breakdown by interfering with FcγR-mediated destruction of opsonised platelets86,87 (Figure 4). Published studies have confirmed a response rate of 43% in patients who were previously heavily pretreated. The durable response rate
was reported at 18%. This rate may be higher if fostamatinib is used earlier. Adverse events reported in the studies include hypertension in 28%, and diarrhoea in 31% of the subjects, respectively. These adverse events were predominantly mild to moderate.

So, currently there are two new approved classes of therapy for ITP, namely the TPO-RAs and a syk inhibitor. But yet further classes of therapy are in advanced stages of clinical development including drugs active against the neonatal Fc receptor (anti-FcRn), Bruton tyrosine kinase inhibitors and complement inhibitors. We will discuss these briefly here.

Treatments in clinical development

Anti-FcRn
The neonatal Fc receptor modulates the half-life of IgG and albumin. It does this by binding to IgG and releasing it from endothelial endosomes. As well as recycling normal IgG, the FcRn also recycles pathologic IgG. Blocking the FcRn causes IgG breakdown within the endosomes. Two molecules are currently in advanced phase clinical development: rozanolixizumab (UCB) and efgartigimod (argenx) (Figure 4).

In phase 2 studies, both efgartigimod and rozanolixizumab were well tolerated and responses of 38% (efgartigimod) and 50% (rozanolixizumab) were seen. Phase 3 studies of both agents are ongoing. Data thus far would appear to indicate that although the IgG levels fall this does not appear to increase the risk of infection.

Bruton tyrosine kinase inhibitors (BTKIs)
Bruton tyrosine kinase, like syk, is involved in Fcγ signalling and is another potential target for ITP therapy (Figure 4). BTK is necessary for B cell development, function and antibody production. Several BTKIs have been developed for diseases such as chronic lymphocytic leukaemia. However, BTKIs have been reported to inhibit platelet aggregation which may result in bleeding, which is a concern in ITP. Although this was reported with ibrutinib it is not the case with rilzabrutinib.

Results from a recent Phase 2 study of rilzabrutinib in adult patients with relapsed or refractory ITP have been published. Fifty nine adults, who had at least one prior response to treatment and a platelet count ≤50 × 10⁹/L, were given oral rilzabrutinib at 200 or 400mg daily or 300 or 400mg twice daily. The highest response rate was seen in the 400mg twice daily group. Of 44 patients on this dose 39% achieved the primary endpoint (two or more platelet counts ≥50 × 10⁹/L without the use of rescue therapy). Of the 33 patients...
who completed the study for more than 12 weeks, 17 of these (52%) responded. Of the responders half of these (50%) achieved a platelet count $\geq 30 \times 10^9/L$ by day 8. Rilzabrutinib was well tolerated with adverse events of Grade 1 or 2 only.

The complement system

Complement is believed to be involved in the pathogenesis of ITP for some patients. However, the contribution made by complement to ITP is not clearly understood. Early phase studies with sutimlimab, a monoclonal IgG C1s inhibitor, have been conducted. The patients treated were adults with ITP for $>1$ year and an inadequate response to $\geq 2$ prior treatments. A total of 12 patients were treated of which 42% responded (platelet count $\geq 50 \times 10^9/L$). Four patients (33%) achieved a platelet count of $\geq 50 \times 10^9/L$ for \textless 70% of their study visits. One third of patients responded in two days or less. No treatment-related adverse events were noted (Figure 4). Anti-CD40L treatment may be useful for some with refractory ITP which may be caused by long-lived plasma cells. Anti-CD38 treatment may be useful for some with refractory ITP which may be caused by long-lived plasma cells. Other treatments in development

A number of other molecules are being developed. This includes other TPO receptor agonists lusutrombopag and heterombopag, as well as an anti-CD38 molecule (daratumumab), and others (Figure 4). Anti-CD38 treatment may be useful for some with refractory ITP which may be caused by long-lived plasma cells.

Conclusions

ITP has a complex and ill-defined pathophysiology. Basic science and the need to avoid the less effective immune suppressants, has led to the development of new more targeted treatments for ITP, starting with the second generation TPO-RAs and now include syk inhibition with other classes of treatment in clinical development. The introduction of these novel therapies has allowed us to use less immune suppression in ITP management. Over the last decade there has been a shift away from immune suppression for the treatment of ITP. However, the COVID-19 pandemic has forced our hand in speeding up this move towards less immune suppressive treatments. As a result of this, the patients' quality-of-life has improved since drugs like TPO receptor agonists have high efficacy and are well tolerated. Once the drugs undergoing development are approved it is likely that there will be a much reduced reliance on
the older empirical immune suppressive therapies. These new drugs also appear to offer patients a much higher chance of a treatment-free sustained response than with the older immune suppressants. Some of these “remissions” may be cures but we need much longer follow-up of the patients and good basic science studies.

Outstanding questions
Primary ITP is now recognized as an autoimmune syndrome with several types of underlying mechanisms. Unfortunately there are no specific assays to distinguish such differing pathogeneses and for this reason all patients with ITP are treated the same; phenotypically they look similar. Treatment until recently has been unsatisfactory and empirical but over the last 10 years or so patients have been treated with agents that have undergone randomized trials and are fully approved for primary ITP. But there is still great uncertainty in terms of which patients to treat, with which therapy and for how long. Overtreatment remains a problem for patients with ITP and health-related quality of life suffers as a result. We need better stratification of patients in order to avoid treatment in those who do not require this, whilst directing treatment at patients who will benefit. We have few licensed therapies currently but the list is growing with a number of very promising treatments undergoing clinical trials.

Search strategy and selection criteria
Data for this review were collected using PubMed searches between 1990–2021, using the terms “immune thrombocytopenia”, “idiopathic thrombocytopenic purpura”, “ITP”, “pathogenesis”, “pathophysiology”, “treatment”, “management”, “therapy”, “advances”, “novel therapies”.

Declaration of interests
DP has received research support and honoraria from Amgen, Novartis, SOBI, UCB, argenx, Rigel and Chugai and has acted as a consultant for UCB, argenx, MedImmune and Ono; he also serves on a DSMB for an investigator-led study of rituximab in ITP and has received a basic shares package from previous employment by GlaxoSmithKline. JWS has received honoraria from Amgen, Novartis, and UCB and has acted as a consultant for Amgen, Novartis, Argenx and UCB.

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Contributors
Drew Provan: performed literature search, drafted 50% of the manuscript and drew the figures, proofread the entire manuscript. John W Semple: performed literature search, drafted 50% of the manuscript, helped design the figures, proofread the entire manuscript. Both authors read and approved the final version of the manuscript.

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