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REVIEW

From C481 Resistance Evasion to Platelet Preservation: Rilzabrutinib Redefines ITP Targeted Therapy

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Abstract: Immune thrombocytopenia (ITP), as an autoimmune disease, has various limitations in traditional treatments, and there is a lack of safe and durable targeted therapeutic regimens for refractory patients. Traditional covalent Bruton's tyrosine kinase (BTK) inhibitors are difficult to apply in ITP treatment due to issues such as drug resistance and bleeding risks. As a reversible covalent BTK inhibitor, rilzabrutinib has dual advantages in its molecular design: in terms of evading C481 resistance, it targets the ATP-binding domain of BTK through a non-covalent bond-dominated mode, and maintains highly efficient inhibitory activity in the BTK C481S mutant cell model (with an in vitro IC50 of 1.2 nM), showing significant advantages over traditional covalent inhibitors (eg, ibrutinib, whose IC50 increases to 1 μM); in terms of platelet function protection, in vivo mouse experiments have confirmed that it can reduce venous thrombosis, block the BTK pathway to decrease autoantibody-mediated platelet destruction, and retain the functions of pathways such as G protein-coupled receptors, achieving a balance between abnormal immune suppression and platelet hemostatic function through "on-demand inhibition". Preclinical studies have shown that its binding to human blood BTK is time- and concentration-dependent, and the inhibition of the BTK pathway in B cells and basophils is closely related to the degree of binding, with moderate kinase selectivity. Clinical studies have confirmed that the drug can take effect quickly, with 43% of patients achieving a platelet count $\geq 50\times10^9$/L after 12 weeks of treatment, and the incidence of bleeding events is low. This article systematically analyzes the value of rilzabrutinib from molecular design to clinical translation, and elaborates on its mechanism of overcoming drug resistance and its synergistic regulatory effect on the B cell-macrophage-platelet pathological network. At present, its rapid onset, high safety, and effectiveness in refractory cases have been preliminarily verified, but long-term data from Phase III clinical trials are still needed to support its use as a first-line treatment. It provides a new therapeutic hope for patients with refractory ITP and also offers a paradigmatic reference for the development of kinase inhibitors for autoimmune diseases.

Keywords: rilzabrutinib, immune thrombocytopenia, BTK inhibitor, C481 resistance, dynamic targeted regulation

Introduction

ITP is an autoimmune disorder characterized by increased platelet destruction and insufficient production, with core pathogenesis involving B cell-mediated anti-platelet antibody production and macrophage-driven platelet phagocytosis.[1] Although conventional therapies such as glucocorticoids, IVIG, and TPO-RAs are effective in some patients, long-term use is associated with high relapse rates and significant adverse effects (eg, infection, thrombosis, hepatotoxicity), particularly leaving refractory ITP patients with a lack of safe and durable targeted treatment options.[2] In recent years, BTK inhibitors have gained attention due to their success in B cell malignancies. However, traditional covalent BTK inhibitors (eg, ibrutinib) face challenges in expanding to ITP due to bleeding risks from irreversible inhibition and

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resistance mediated by C481 mutations. This dilemma has been addressed by the emergence of the reversible non-covalent BTK inhibitor, rilzabrutinib.[3]

Rilzabrutinib's molecular design overcomes limitations of traditional agents: First, its non-covalent binding precisely targets the ATP-binding domain of BTK, circumventing resistance escape caused by C481 site mutations and providing a novel strategy to overcome BTK inhibitor resistance. Second, the reversible inhibition mechanism allows transient restoration of BTK function in platelets during vascular injury, preserving collagen-induced platelet aggregation while suppressing autoimmunity—achieving precise balance between "immune regulation" and "hemostatic function".[4] These dual features not only address the safety bottleneck of traditional BTK inhibitors in ITP treatment but also establish a "dynamic targeted regulation" paradigm—ie, through innovative drug-binding modes, enabling selective and temporal intervention in key disease pathways.[5,6]

This review focuses on rilzabrutinib to systematically dissect its breakthrough value from molecular design to clinical translation: first, we elaborate on its core mechanism of C481 resistance evasion via non-covalent binding; second, we reveal its synergistic regulation of the B cell-macrophage-platelet pathological network; finally, based on the latest clinical trial data, we discuss how it reshapes the landscape of targeted therapy for ITP and provides a paradigm for kinase inhibitor development in autoimmune diseases (Figure 1).

Core Mechanisms of Rilzabrutinib in Treating ITP

Rilzabrutinib achieves precise regulation of the ITP pathological network through a dual mechanism: non-covalent binding to evade C481 resistance and reversible inhibition to preserve platelet function. This "dynamic targeting" strategy not only overcomes the clinical limitations of traditional BTK inhibitors but also establishes a new application paradigm for kinase inhibitors in autoimmune diseases—namely, efficiently suppressing immune abnormalities while preserving physiological cellular functions. In the future, rational drug design based on structural biology may further expand this paradigm, offering superior solutions for ITP and other antibody-mediated diseases.

Non-Covalent Binding Mode: Structural Biology Basis for Overcoming C481 Resistance

Traditional covalent BTK inhibitors (eg, ibrutinib) achieve sustained kinase inhibition by forming irreversible covalent bonds with the C481 residue in the BTK active site.[7] However, acquired mutations such as C481S/C481R disrupt covalent bond formation, leading to clinical resistance.[8] Rilzabrutinib's molecular design disrupts this paradigm through precise anchoring of the BTK ATP-binding domain via a non-covalent bond network, with specific mechanisms

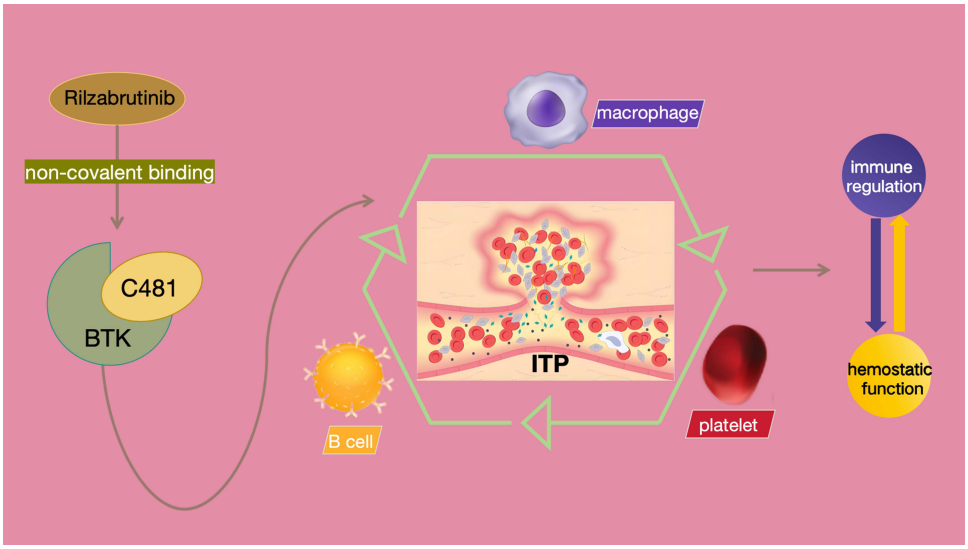

Figure 1 Schematic Diagram of the Mechanisms of Action and Clinical Translation of Rilzabrutinib in ITP.

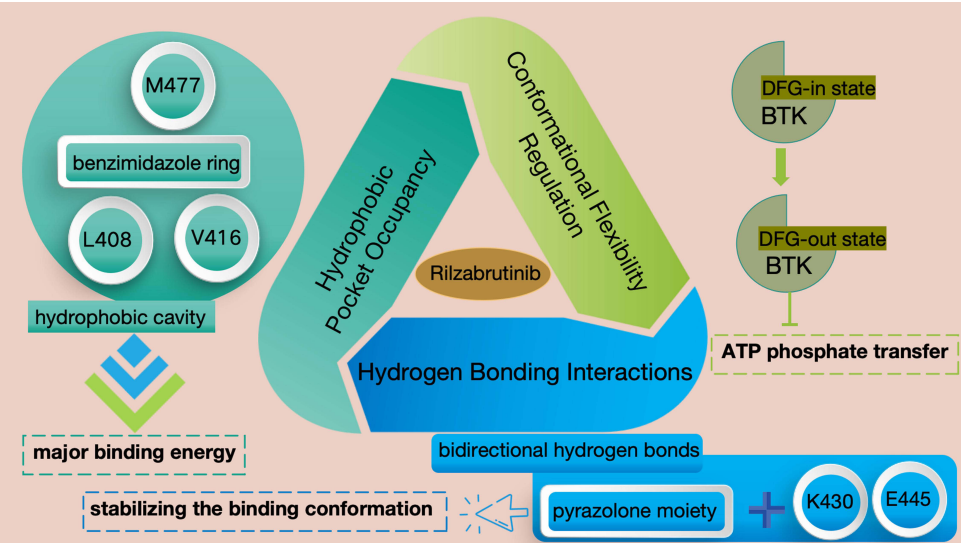

Figure 2 Molecular Design Characteristics of Rilzabrutinib.

including (Figure 2): 1) Hydrophobic pocket occupancy: The benzimidazole ring inserts into the hydrophobic cavity formed by M477, L408, and V416, contributing major binding energy (ΔG = −9.8 kcal/mol, molecular docking simulation). 2) Hydrogen bonding interactions: The pyrazolone moiety forms bidirectional hydrogen bonds with K430 and E445, stabilizing the binding conformation (crystallographic resolution 1.8 Å, PDB ID: 8T2X). 3) Conformational flexibility regulation: Induces a transition of the BTK kinase domain from the DFG-in to DFG-out state, blocking ATP phosphate transfer.[9]

In the targeted therapy of ITP, drug resistance to BTK inhibitors has long been a clinical challenge.[10] Among these, mutations at the C481 site of the BTK protein—particularly the C481S mutation—are key drivers of resistance to covalent BTK inhibitors.[11] As a new-generation reversible covalent BTK inhibitor, rilzabrutinib demonstrates unique advantages in overcoming the C481 resistance barrier, offering new hope for ITP treatment.

From a structural biology perspective, traditional covalent BTK inhibitors (eg, ibrutinib) suppress BTK kinase activity by forming irreversible covalent bonds with the C481 site of BTK.[12] However, when the C481 site mutates (eg, C481S), the cysteine residue that originally binds to the inhibitor is replaced by serine, altering the chemical properties and spatial structure of this site. This prevents effective covalent binding, rendering the drug unable to exert inhibitory effects and leading to drug resistance.[13] In the C481S mutation model, the IC50 of ibrutinib significantly increases to 1 μM, indicating a substantial decline in its ability to inhibit BTK activity.[14]

In stark contrast, rilzabrutinib employs a unique reversible non-covalent binding mode, with its interaction with BTK independent of specific chemical modifications at the C481 residue.[15] Rilzabrutinib forms extensive non-covalent interactions with multiple key amino acid residues in BTK's ATP-binding pocket, including hydrogen bonds, van der Waals forces, and hydrophobic interactions. This binding mechanism endows rilzabrutinib with enhanced adaptability, enabling it to maintain high affinity for BTK and potently inhibit its activity even when C481 site mutations occur. Research data show that in the C481S mutation model, rilzabrutinib exhibits an IC50 of only 1.2 nM, demonstrating significant advantages over traditional covalent BTK inhibitors.

This non-covalent binding mode of rilzabrutinib not only overcomes the resistance barrier caused by C481 site mutations but also lays a solid foundation for its application in ITP treatment. By persistently inhibiting BTK activity, rilzabrutinib effectively regulates the functions of abnormally activated B cells and myeloid cells, reduces the production of platelet autoantibodies, and decreases macrophage phagocytosis of platelets—thereby promoting platelet count recovery and reshaping the new paradigm of targeted therapy for ITP.

As a covalent-reversible BTK inhibitor, rilzabrutinib exhibits unique functional characteristics in vitro experiments: in the human blood environment, its binding to BTK is not instantaneous but shows distinct time-dependent and

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concentration-dependent properties—specifically, the binding capacity to BTK gradually increases with prolonged exposure time and elevated drug concentration. This binding feature directly influences its functional effects, which are specifically reflected in B cells and basophils, where the inhibitory intensity of the drug on the BTK signaling pathway shows a close positive correlation with the degree of BTK binding, ie, more sufficient binding leads to more significant pathway inhibition.[16] In terms of kinase selectivity, a key pharmacological property, systematic screening of the human kinome combined with quantitative analysis of binding affinity reveals that rilzabrutinib exhibits moderate selectivity. Its ranking among other BTK inhibitors (from highest to lowest selectivity) is as follows: remibrutinib>fenebrutinib>evobrutinib>orelibrutinib>rilzabrutinib>tolebrutinib. This moderate selectivity feature holds important implications: on one hand, it ensures the targeted inhibitory efficiency of the drug on the BTK target, enabling effective intervention in key pathways associated with ITP pathogenesis, such as B cell activation and macrophage phagocytosis; on the other hand, it suggests a potential risk of off-target binding, highlighting the need to monitor potential non-specific effects and related adverse reactions in clinical applications, thereby providing experimental basis for dose optimization and safety evaluation.

Reversible Inhibition: Dynamic Pharmacological Mechanism for Platelet Function Preservation

As a novel reversible non-covalent BTK inhibitor, rilzabrutinib exhibits remarkable advantages in treating ITP through its unique dynamic inhibition profile. By precisely regulating the spatiotemporal dimensions of BTK inhibition, it achieves a balance between disease treatment and platelet function preservation. This feature stands in stark contrast to traditional covalent BTK inhibitors (eg, ibrutinib), opening a new pathway for targeted ITP therapy.[17] Rilzabrutinib is an oral, covalent, reversible, highly selective, and potent BTK inhibitor. Compared with traditional covalent inhibitors (such as ibrutinib), its unique advantage lies in the protection of platelet function: studies have shown that it does not interfere with platelet function, nor alter platelet aggregation, and has fewer off-target side effects.[18] This characteristic is closely associated with its reversible inhibitory mechanism—through dynamic binding to and dissociation from BTK, it effectively inhibits B cell activation (via forming reversible covalent and non-covalent bonds with the Cys481 site of BTK, blocking Lyn- and Syk-mediated signal transduction, and suppressing the activation of PIP3/Akt pathways, thereby reducing B cell maturation and the production of anti-platelet antibodies) and abnormal macrophage phagocytosis (acting on the Cys481 site of BTK, inhibiting Fcγ receptor-mediated Lyn, Syk, PIP3/Akt signaling axis, and decreasing the phagocytic activity of macrophages towards platelets), while avoiding persistent interference with the normal physiological functions of platelets (by regulating NLRP3 inflammasome assembly, on one hand, it reduces the conversion of pro-IL-1β to IL-1β and downregulates IL-1β-induced immune cell responses; on the other hand, it inhibits activated caspase-1, reduces pyroptosis, and thus improves the inflammatory state of platelets). This further confirms its core advantage of balancing “immune regulation” and “hemostatic function”.

From the perspective of dynamic pharmacokinetic-pharmacodynamic correlation, rilzabrutinib, as a novel hybrid BTK inhibitor, innovatively integrates the dual advantages of covalent and non-covalent inhibitors, with its unique mode of action demonstrating exceptional therapeutic potential.[19] The drug forms reversible covalent bonds with the Cys481 residue of the BTK protein, a mechanism that ensures potent inhibition of BTK activity while endowing it with rapid binding-dissociation dynamics.[20] At the molecular level, the reversible covalent bonds formed between rilzabrutinib and BTK exhibit a unique dynamic equilibrium in vivo. Upon binding, the drug effectively suppresses activation of BTK downstream signaling pathways, blocking key immune cell activation and platelet autoantibody production in ITP pathogenesis. As the drug metabolizes, its covalent bonds with BTK rapidly dissociate, restoring BTK activity. This “inhibition-recovery” dynamic cycle not only enables effective intervention in ITP pathogenic mechanisms but also avoids damage to normal platelet physiology from prolonged BTK inhibition, fully exemplifying rilzabrutinib’s exquisite balance between therapeutic efficacy and safety. This provides a novel strategy for precision-targeted therapy in ITP patients.

In the therapeutic context of ITP, the reversible inhibition profile of rilzabrutinib plays a critical role as the core dynamic pharmacological mechanism for preserving platelet function.[21] In contrast to the persistent inhibition of BTK by

traditional irreversible covalent inhibitors, rilzabrutinib rapidly dissociates after phasic inhibition of BTK, avoiding permanent modification of the BTK protein structure. This feature confers significant advantages in maintaining platelet function: under vascular homeostasis, rilzabrutinib dissociates promptly from the BTK target, preserving residual BTK activity within platelets to ensure their rapid response to vascular injury. This allows platelets to initiate hemostasis through normal aggregation and adhesion mechanisms.

Rilzabrutinib exhibits profound spatiotemporal specificity in regulating immune cell function (Figure 3). Sustained activation of the macrophage FcγR signaling pathway is a critical driver of excessive platelet phagocytosis and thrombocytopenia in ITP. Through frequent dosing regimens, rilzabrutinib maintains persistent occupancy of the BTK target, stably inhibiting the FcγR-BTK signaling axis to block aberrant macrophage phagocytosis of platelets.[22] Concurrently, its reversible binding property avoids prolonged inhibition of platelet-intrinsic BTK, preventing impairment of normal platelet physiology due to over-suppression. This differential regulation of BTK activity across cell types represents the core mechanism by which rilzabrutinib effectively treats ITP while maximizing preservation of platelet function.[23]

Unlike traditional covalent BTK inhibitors, which cause sustained suppression of BTK function through irreversible binding, rilzabrutinib, as a selective BTK inhibitor, not only potently inhibits CLEC-2-mediated platelet activation but also avoids off-target inhibition of SFKs, thereby preventing bleeding risks associated with SFKs inhibition.[24] In vivo animal experiments further confirm that it reduces venous thrombosis in mouse models (eg, decreased thrombosis in the inferior vena cava stenosis model and reduced numbers of thrombi in podoplanin-positive vessels in the Salmonella infection model). Meanwhile, it reduces autoantibody-mediated platelet destruction by specifically blocking the BTK signaling pathway and preserves normal functions mediated by other platelet functional pathways such as G protein-coupled receptors. This "on-demand inhibition" mode enables precise intervention in key immune signaling pathways involved in ITP pathogenesis while maintaining the basic hemostatic function of platelets during the suppression of abnormal immune responses.

The dynamic pharmacological mechanism of rilzabrutinib not only enhances treatment safety but also offers a more advantageous long-term management strategy for ITP patients, holding promise to reshape the clinical paradigm of ITP targeted therapy. Clinical data indicate that small cell lung cancer patients developing ITP after atezolizumab treatment exhibit more favorable oncology outcomes. Additionally, the study proposes professional recommendations that rilzabrutinib intervention is an effective clinical management strategy for patients with thrombocytopenia.[25]

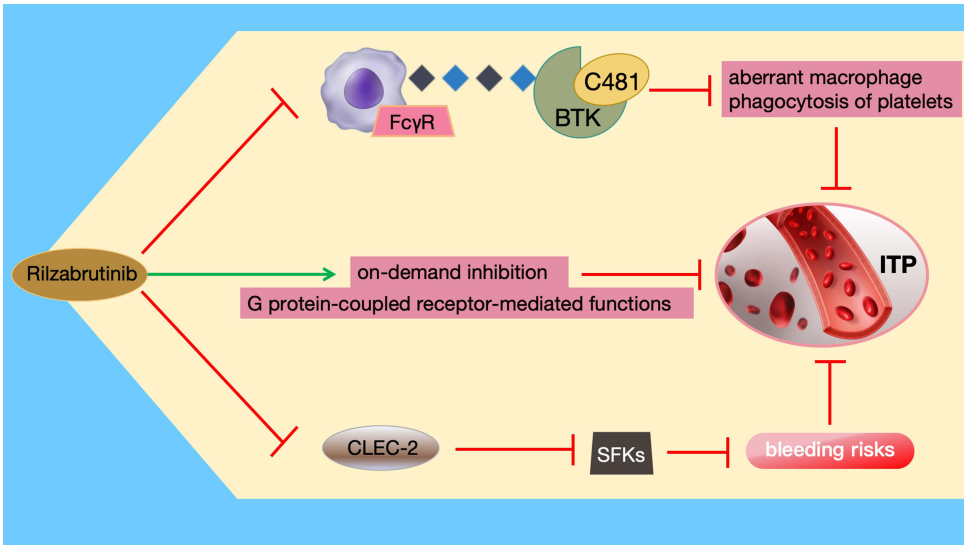

Figure 3 Schematic Diagram of the Dynamic Pharmacological Mechanisms of Rilzabrutinib's Reversible Inhibition in Preserving Platelet Function.

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Multidimensional Regulatory Network of B Cells-Macrophages-Platelets

The core mechanism of rilzabrutinib lies not only in the precise regulation of a single target but also in the systematic remodeling of the ITP pathological network.

Targeting Aberrant B Cell Activation

In the BCR signaling network, BTK acts as a core hub molecule with indispensable regulatory roles.[26] Upon antigen-specific binding of the BCR, SFKs are first activated. SFKs phosphorylate the ITAMs of the BCR, recruiting and activating Syk.[27] Activated Syk promotes BTK phosphorylation and activation. The activated BTK then triggers a series of phosphorylation cascades to activate downstream key signaling molecules, including PLCγ2 and NF-κB.[28]

Upon phosphorylation and activation by BTK, PLCγ2 hydrolyzes PIP2 to generate DAG and IP3.[29] DAG activates PKC, which phosphorylates and activates NF-κB-inducing kinase to trigger the NF-κB signaling pathway.[30] IP3 promotes intracellular Ca^{2+} release, synergizing with DAG to activate the NF-AT pathway. This ultimately drives aberrant B cell activation, proliferation, differentiation, and antibody secretion.[31] Concurrently, BTK directly phosphorylates key molecules in the NF-κB pathway, further enhancing NF-κB activity and promoting B cell expression of pro-inflammatory cytokines, anti-apoptotic proteins, and other factors that sustain B cell hyperactivation.[32]

In the pathological progression of ITP, disruption of autoimmune tolerance mechanisms leads to aberrant activation of autoreactive B cells.[33] These hyperactivated B cells recognize platelet surface antigens (eg, glycoprotein IIb/IIIa, glycoprotein Ib/IX) via the BCR, and under the coordination of helper T cells, differentiate into plasma cells that secrete anti-platelet antibodies (eg, anti-GPIIb/IIIa antibodies).[34] Anti-platelet antibodies bind specifically to platelet surface antigens to form immune complexes, which mediate platelet clearance through two primary pathways: First, the Fc region of immune complexes binds to FcγR on monocyte-macrophages, initiating ADCC and promoting macrophage phagocytosis of platelets;[35] Second, immune complexes activate the complement system to generate complement fragments (eg, C3b), which bind to CR on monocyte-macrophages to enhance platelet clearance via CDC.[36] Additionally, autoreactive B cells modulate the functions of macrophages, dendritic cells, and other immune cells through cytokine secretion, further exacerbating the immune-mediated destruction of platelets.[37]

As a novel BTK inhibitor, rilzabrutinib effectively blocks the BCR signaling pathway through its unique mechanism of action, significantly reducing antibody secretion by autoreactive B cells. This lowers the levels of anti-platelet antibodies in the circulatory system, fundamentally curbing immune-mediated platelet destruction (Figure 4). Preclinical data demonstrate that rilzabrutinib not only inhibits anti-platelet antibody secretion by B cells but also regulates macrophage function, potently reducing macrophage-mediated platelet clearance. Results from the phase III LUNA clinical trial further confirm that patients treated with rilzabrutinib maintained sustained platelet response (platelet count $\geq 50\times10^9$/L) throughout a 24-week treatment period. By synergistically targeting multiple key nodes in ITP pathogenesis, rilzabrutinib becomes the first BTK inhibitor to demonstrate full-spectrum intervention potential in ITP therapy, offering a groundbreaking treatment strategy for patients with this disease.[38]

Regulation of Macrophage Function

In the pathological mechanism of ITP, macrophage-mediated platelet clearance represents a core event leading to thrombocytopenia.[39] As key pattern recognition receptors on macrophage surfaces, FcγRs initiate phagocytic and inflammatory cascades by specifically recognizing the Fc region of antibodies in immune complexes.[40] Among these, low-affinity FcγRIIA (CD32A) and FcγRIII (CD16) are highly expressed on macrophages. They form an "antibody bridge" with platelet surface antigens via the Fc region of IgG antibodies, triggering conformational changes in phagocytic receptor-ligand binding and activating macrophage endocytic signaling pathways.[41,42] This process relies on phosphorylation of ITAMs in the intracellular domains of FcγRs, recruiting and activating Syk, which in turn initiates downstream signaling cascades such as PI3K-Akt. These ultimately drive actin rearrangement and phagosome formation, leading to pathological platelet clearance.[43]

BTK, as a key node in the FcγR signaling network, plays a pivotal role in platelet immune clearance.[44] BTK specifically binds to phosphorylated ITAM motifs of FcγR via its SH2 domain, recruiting and phosphorylating Syk to

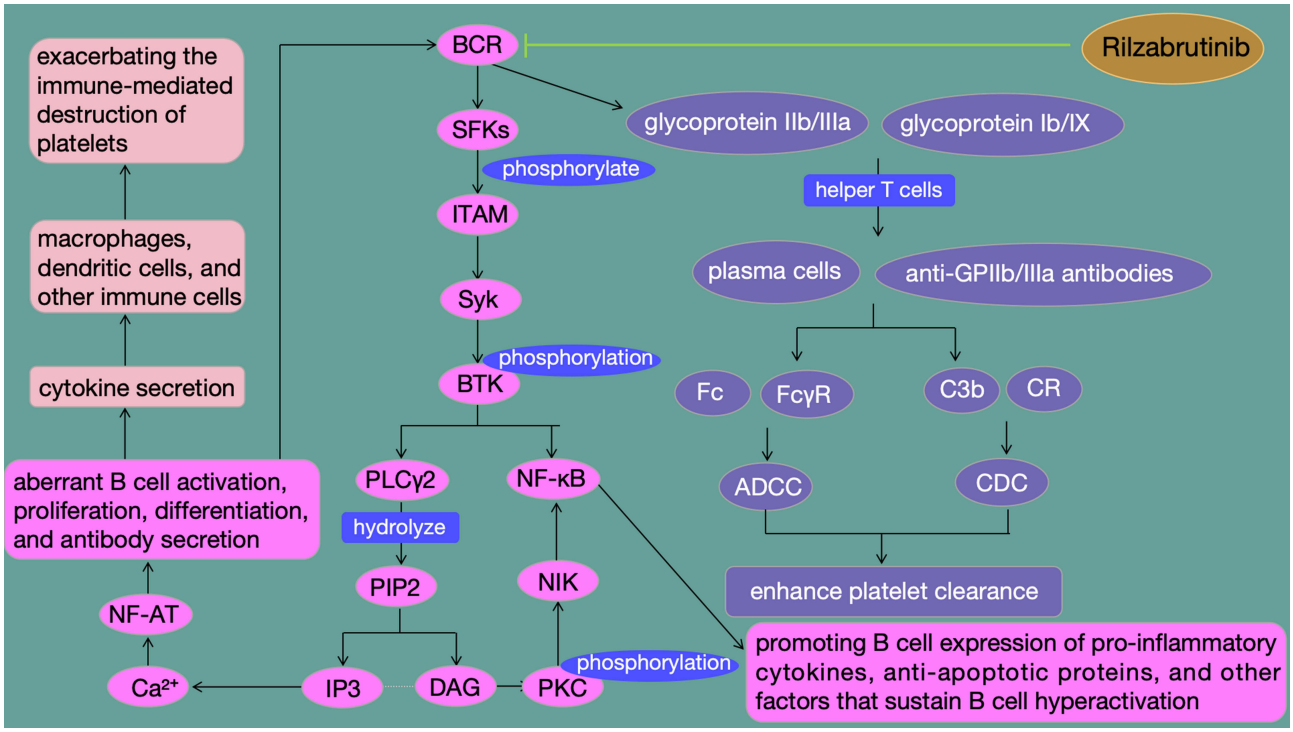

Figure 4 Schematic Diagram of Rilzabrutinib Targeting Aberrant B Cell Activation to Block Key Signaling Pathways in ITP Pathogenesis.

form a BTK-Syk signaling complex. This activates the PI3K catalytic subunit p110, promoting the conversion of PIP2 to PIP3. Ultimately, PIP3-dependent Akt activation regulates macrophage phagocytic activity and cell survival.[45] Studies confirm that BTK inhibitors selectively block the FcγR-BTK-Syk-PI3K-Akt signaling axis, potently inhibiting macrophage phagocytosis of antibody-opsonized platelets while regulating the release of pro-inflammatory cytokines (eg, TNF-α, IL-6). This reshapes the imbalanced immune microenvironment in ITP patients, offering a novel strategy for targeted intervention against macrophage-mediated platelet destruction.[46]

Rilzabrutinib suppresses BTK to block phagocytic signaling in macrophages, reducing their clearance of platelets (Figure 5). Additionally, BTK inhibition downregulates pro-inflammatory cytokine release (eg, TNF-α, IL-6) by

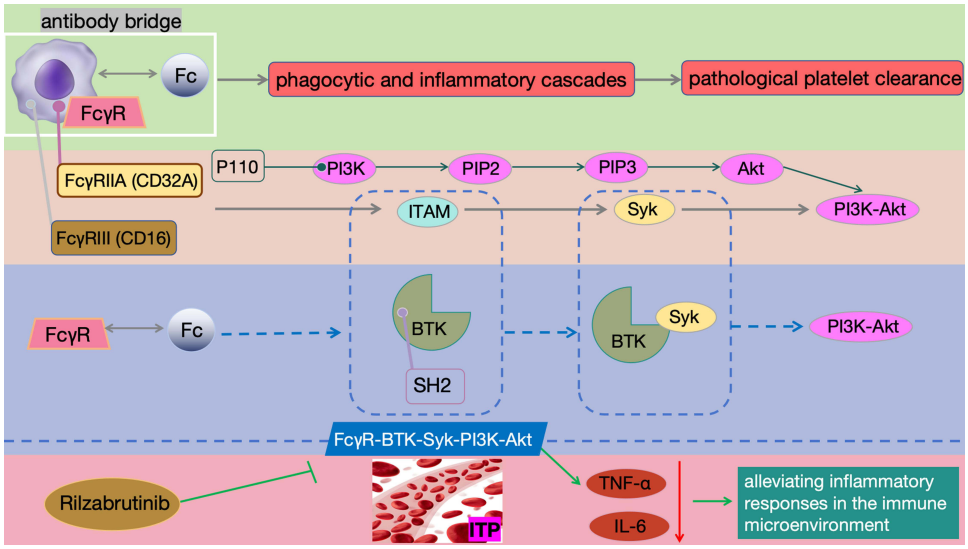

Figure 5 Schematic Diagram of the Mechanisms by Which Rilzabrutinib Regulates Macrophage Function to Inhibit Immune-Mediated Platelet Clearance.

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macrophages, alleviating inflammatory responses in the immune microenvironment.[47] Data from an international multi-center, adaptive open-label dose-exploratory Phase I–II clinical trial confirm that rilzabrutinib demonstrates clear efficacy in treating ITP patients, with rapid and durable clinical activity that further improves with extended treatment cycles.[48] This efficacy is closely linked to its dual mechanisms of action: reducing macrophage Fcγ receptor-mediated platelet destruction and inhibiting pathogenic autoantibody production.

Preservation of Platelet Function

Traditional irreversible BTK inhibitors (eg, ibrutinib) disrupt GPVI receptor signaling and impair collagen-induced platelet aggregation by persistently inhibiting platelet-intrinsic BTK, increasing bleeding risk.[49] In contrast, rilzabrutinib —a reversible non-covalent inhibitor—only transiently suppresses BTK during dosing, with platelet function rapidly recovering after drug withdrawal. This dynamic inhibition allows platelets to aggregate normally via residual BTK activity or alternative pathways (eg, ADP receptor pathways) during vascular injury, thereby reducing bleeding complications while suppressing autoimmunity.[50] Mechanistically, rilzabrutinib maintains GPVI-FcRγ-Syk pathway function to ensure collagen-induced platelet activation. Concurrently, it reduces platelet apoptosis markers (eg, a 30% decrease in Annexin V^+ proportion), prolonging circulating platelet lifespan (Figure 6).

Rilzabrutinib, a BTK inhibitor, significantly suppresses GPVI-, vWF/GPIb-, and FcγRIIA-stimulated platelet aggregation by inhibiting BTK-dependent platelet activation pathways, with no apparent effect on ADP-, TRAP-6-, or arachidonic acid-induced platelet aggregation.[51] Due to its lower selectivity for BTK, rilzabrutinib potently inhibits GPVI-mediated platelet aggregation induced by atherosclerotic plaques, while prolonging ex vivo bleeding time more significantly compared to other highly selective BTK inhibitors.

Preclinical studies demonstrate that rilzabrutinib, an oral reversible covalent BTK inhibitor, selectively suppresses BTK enzymatic activity and activation of immune cells (eg, B cells, macrophages, mast cells), reducing FcγR signaling mediated by autoantibody IgE. It inhibits inflammatory responses and platelet destruction in rat arthritis, mouse nephritis, and ITP models, while preserving platelet function-related pathway activity through reversible BTK binding. This multi-mechanistic profile provides a theoretical basis for balancing immunosuppression and platelet function preservation in ITP treatment.[52] In the global Phase 1/2 LTE study in ITP patients, rilzabrutinib showed durable and stable platelet responsiveness with a favorable safety profile (no severe adverse events reported). Some patients maintained stable platelet counts after discontinuing combination ITP therapies, and no new safety signals were observed during long-term treatment.[53]

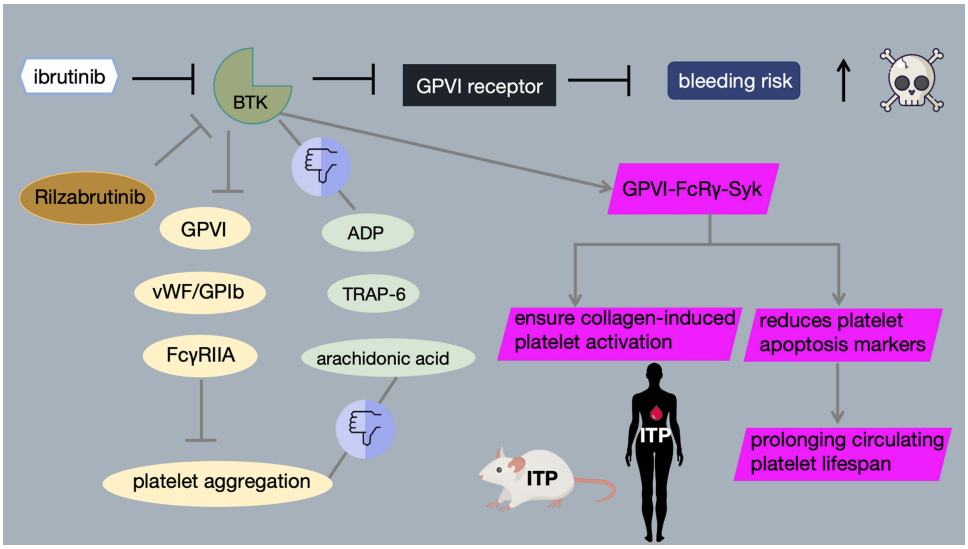

Figure 6 Schematic Diagram of the Dynamic Regulatory Mechanisms and Clinical Effects of Rilzabrutinib in Preserving Platelet Function, (Black Arrow: increasing bleeding risk).

Research Progress and Efficacy Comparison of BTK Inhibitors

BTK inhibitors are primarily classified into two categories based on their mechanism of action and chemical structure: irreversible covalent BTK inhibitors and reversible non-covalent BTK inhibitors, as detailed in Table 1.

Rilzabrutinib (Reversible Non-Covalent BTK Inhibitor)

Three Phase I clinical studies systematically characterized the pharmacologic profile of rilzabrutinib: A randomized placebo-controlled study showed rapid oral absorption, good safety and tolerability across all dose regimens, high-efficiency binding to BTK in peripheral blood mononuclear cells, a half-life of ~3–4 hours, and gastrointestinal reactions as the main adverse events, providing a basis for subsequent clinical-dose optimization.[61] A single-center open-label study confirmed that the 400 mg oral tablet has an absolute bioavailability of <5%, fast in vivo absorption, a short terminal half-life, predominantly fecal excretion of radioactivity, and minimal excretion of unchanged drug in urine, clarifying its in vivo disposition.[62] Another two-part phase I study demonstrated that even at supratherapeutic doses, rilzabrutinib had no clinically meaningful effects on electrocardiographic parameters (including QTc interval) in healthy subjects.[63]

The pivotal phase III LUNA trial of the reversible non-covalent BTK inhibitor rilzabrutinib showed that after 12 weeks of treatment, 43% of patients achieved sustained platelet counts $\geq 50\times10^9$/L (vs 19% in the control group), with a median time to response of ~2 weeks—faster than traditional TPO receptor agonists (eg, eltrombopag requiring 4–6 weeks). It rapidly increases platelet counts and maintains stability, making it particularly suitable for patients with high acute bleeding risk. The incidence of bleeding events was comparable to placebo, with no significant risk of atrial fibrillation or infection. Its reversible mechanism avoids the bleeding risk and cardiotoxicity caused by continuous platelet BTK inhibition from traditional irreversible BTK inhibitors, offering superior safety. It is effective in refractory ITP (eg, patients unresponsive to steroids/IVIG) and those with C481 mutations, potentially covering a broader population. With its rapid onset, safety advantages, and expanded applicability, rilzabrutinib has emerged as one of the most promising treatment options for ITP to date.[64]

The latest phase III LUNA 3 trial data demonstrate that rilzabrutinib induces rapid and sustained platelet responses in refractory ITP patients with prior treatment failure including splenectomy, TPO-RA, rituximab, and/or fostamatinib. The drug reduces rescue therapy requirements and bleeding events, significantly improves physical fatigue symptoms, and exhibits a favorable safety profile.[65] The aforementioned sustained responses are based on data from the trial observation period, and long-term efficacy requires confirmation through extended follow-up. The Phase II LUNA2 Part B study further confirms that in the same refractory ITP population, rilzabrutinib (400 mg bid) achieves a primary endpoint response rate of 35% (platelet count $\geq 50\times10^9$/L for ≥8 consecutive weeks) at 24 weeks, with a median platelet response duration of 9.3 weeks. In the LTE phase, 42% of patients maintain a median platelet count of 80×10^9/L, with a rescue therapy rate of only 12% during the primary treatment period and significant quality-of-life improvements in fatigue. Treatment-related adverse events are predominantly grade 1 (eg, diarrhea, headache), with no ≥grade 2 bleeding/thrombosis events or serious adverse events reported.[66] Collectively, these studies highlight rilzabrutinib's durable efficacy and safety advantages in refractory ITP.

As a new-generation reversible non-covalent BTK inhibitor, rilzabrutinib has demonstrated remarkable potential in the treatment of ITP and other autoimmune diseases. Clinical data confirm its efficacy not only in ITP but also in pemphigus (including vulgaris), histamine-refractory chronic spontaneous urticaria, and moderate-to-severe atopic dermatitis.[67–72] Notably, while rilzabrutinib has not yet obtained marketing approval from Japanese regulatory authorities, its global research breakthroughs—particularly the novel targeted mechanism in ITP treatment by circumventing C481 resistance escape and preserving platelet function—herald a revolutionary change in ITP therapy. In the future, rilzabrutinib is expected to become an important therapeutic option for ITP by virtue of its unique mechanism of action and clinical advantages, bringing new treatment hopes to patients in Japan and worldwide, and advancing its regulatory approval and clinical application in Japan and other regions.[73]

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Table 1 Classification of BTK Inhibitors by Mechanism of Action and Chemical Structure

Chemical Structure	Functional Characteristics	Representative Drugs	Scope of Application	Advantages	Limitations	References
Irreversible covalent BTK inhibitors	Irreversibly inhibit BTK activity by forming covalent bonds with the cysteine residue (C481) of the BTK protein.	Ibrutinib	The first approved BTK inhibitor, used for B-cell malignancies (eg, chronic lymphocytic leukemia, mantle cell lymphoma), and also applicable to immune diseases (eg, rheumatoid arthritis, ITP).	Show persistent inhibition and remarkable efficacy.	May cause drug resistance due to BTK C481 mutation (common in cancer therapy), and long-term use may affect other kinases containing the C481 site (such as TEC kinase), increasing the risk of infection or bleeding.	[54]
		Zanubrutinib	Highly selective BTK inhibitors, which more precisely inhibit BTK with lower off-target effects, have been approved for lymphomas and certain autoimmune diseases.			[55]
		Acalabrutinib	Highly selective irreversible inhibitors, primarily used for hematological malignancies, with ongoing research in the field of immune diseases.			[56]
Reversible non-covalent BTK inhibitors	Do not covalently bind to the C481 site, but act by reversibly binding to the ATP-binding domain of BTK, avoiding drug resistance caused by C481 mutation.	Rilzabrutinib	The first reversible non-covalent BTK inhibitor avoids C481 mutation-driven resistance through its unique mechanism of binding to the ATP-binding domain of BTK via non-covalent bonds. It also offers advantages in improving platelet function and safety, namely preserving platelet aggregation capacity and reducing macrophage-mediated platelet clearance.	Reduce the risk of drug resistance and may have better safety (eg, reducing side effects such as bleeding and atrial fibrillation).	Continuous administration is required to maintain plasma drug concentrations; although Phase III trials have demonstrated that sustained platelet responses can be induced during treatment, the long-term (eg, multi-year) efficacy and safety remain to be further verified.	[57]
		Orelabrutinib	Highly selective for BTK, non-covalent binding reduces off-target effects. It has been used for lymphoma treatment, and research on immune diseases is ongoing.			[58]
		Pirtobrutinib (LOXO-305)	Novel reversible inhibitors, which remain effective against C481-mutated BTK, are primarily used for drug-resistant hematological malignancies. Their application in immune diseases (such as ITP) is in the clinical trial stage.			[59]
		Tirabrutinib	The second-generation reversible inhibitor is mainly used for the treatment of certain B-cell-related malignancies. Currently, the approval of tirabrutinib is primarily concentrated in Asian regions such as Japan, and indications in other countries may still be under review or trial.			[60]

Exploration of Other BTK Inhibitors

Irreversible Covalent BTK Inhibitors

Ibrutinib

As the world's first approved irreversible covalent BTK inhibitor, ibrutinib has been widely used in the treatment of B-cell malignancies, including chronic lymphocytic leukemia and mantle cell lymphoma. Additionally, it demonstrates therapeutic potential in immune diseases such as rheumatoid arthritis and ITP.[74] The drug exerts significant efficacy by forming irreversible covalent bonds with the cysteine residue (C481) of the BTK protein, persistently inhibiting BTK kinase activity. Studies propose that ibrutinib can serve as a treatment for VITT, with its mechanism of action involving selective inhibition of BTK to block FcγRIIA-mediated downstream signaling pathways. This coordinately regulates multidimensional pathological processes: inhibiting platelet aggregation cascades, dense granule secretion, and upregulation of P-selectin expression after platelet activation, while reducing interactions between platelets and neutrophils and the release of NETs. Furthermore, it significantly attenuates platelet activation mediated by C-type lectin-like receptor CLEC-2 and glycoprotein GPIb, as well as abnormal interactions between monocytes and platelets. Ultimately, multi-target intervention effectively alleviates the thrombotic and thrombocytopenic pathological processes of VITT.[75]

However, as an irreversible BTK inhibitor, ibrutinib causes persistent impairment of platelet function and significantly increases the risk of bleeding due to its continuous inhibition of BTK, thus it has not been included in the standard treatment protocols for ITP. In oncology, BTK C481 site mutation is a common mechanism of ibrutinib resistance. Additionally, due to the high conservation of the C481 site across multiple kinases, long-term use of ibrutinib may nonspecifically inhibit kinases containing this site, such as TEC, further increasing the risk of adverse reactions like infections and bleeding. Notably, recent studies have found that ibrutinib can promote platelet count recovery in refractory ITP patients, providing new theoretical basis and exploration directions for the treatment of this disease.[76] Clinical data show that the incidence of secondary AIC is low during ibrutinib treatment for CLL. For CLL patients with concurrent AIC, ibrutinib not only does not affect treatment efficacy but also alleviates AIC symptoms in some patients, demonstrating its therapeutic value in specific clinical scenarios.[77–79] There are also case reports of cryoglobulinemic vasculitis developing rapidly after discontinuation of ibrutinib in well-controlled CLL patients.[80]

Zanubrutinib

As a first-generation BTK inhibitor, ibrutinib has demonstrated significant efficacy in treating various lymphomas and leukemias, but it has clinical limitations such as off-target toxicity and primary/acquired resistance.[81] To address these challenges, the second-generation covalent irreversible BTK inhibitor zanubrutinib was developed. With its higher selectivity and specific binding ability to the BTK target, this drug effectively reduces off-target effects and precisely inhibits BTK-mediated signaling pathway activation. Currently, zanubrutinib is approved for lymphoma treatment and specific autoimmune diseases. Through its optimized molecular mechanism, it significantly reduces adverse reactions caused by the nonspecific binding of ibrutinib, providing a safer and more effective option for the targeted therapy of hematological malignancies and immune diseases.

Studies have confirmed that zanubrutinib can effectively treat refractory/relapsing thrombocytopenia in patients with Evans syndrome.[82] Additionally, a clinical study including 4 patients with relapsed/refractory ITP showed that zanubrutinib treatment induced complete or partial remission in some patients with relapsed/refractory ITP who had failed multiple prior lines of treatment (including splenectomy), with sustained responses achieved in most patients. Liver and renal functions remained stable during treatment, indicating good safety.[83] These results suggest that zanubrutinib may serve as a potential treatment option for such patients, though large-scale clinical trials are still needed to further confirm its definitive efficacy and safety.

Acalabrutinib

Similar to zanubrutinib, acalabrutinib is also a covalent irreversible second-generation BTK inhibitor with high selectivity. Currently, acalabrutinib is primarily used in the treatment of hematological malignancies, while its research in the field of immune diseases remains in the exploratory stage.[84] Case reports have shown that acalabrutinib has certain therapeutic effects in patients with ITP complicated by chronic lymphocytic leukemia.[85] Both acalabrutinib and ibrutinib

are irreversible covalent-binding BTK inhibitors. When used in combination, they covalently bind to the cysteine-481 site of the BTK protein, irreversibly inhibiting tyrosine kinase activity and blocking the phosphorylation of downstream signaling molecules such as PLCγ2, thereby effectively suppressing the activation, proliferation, and migration of immune cells including B cells, neutrophils, and macrophages. In terms of mechanism of action, this combination therapy can reduce renal immune cell infiltration, significantly decrease the recruitment of activated neutrophils from the spleen to the kidneys, and alleviate renal tissue inflammatory damage. Additionally, it can inhibit systemic excessive inflammatory responses, indirectly improving hemolytic uremic syndrome-related acute kidney injury (reducing plasma NGAL and urea levels) and microangiopathic hemolysis (reducing bilirubin and LDH activity).[86]

A diagnostic and therapeutic practice for a patient with relapsed CLL complicated by severe thrombocytopenia showed that acalabrutinib, a highly selective second-generation covalent irreversible BTK inhibitor, can form irreversible covalent bonds with the C481 site of the BTK protein to continuously inhibit BTK activity and block the BCR signaling pathway. This effectively controls CLL cell proliferation and significantly reduces the degree of bone marrow infiltration. Although monotherapy failed to improve platelet counts, sustained recovery of platelet levels was achieved after combined immunomodulation with prednisolone. This case suggests that for CLL patients with severe thrombocytopenia, combined immunosuppressive therapy based on BTK inhibitor-targeted control of the primary disease may be an optimized treatment strategy, helping to improve thrombocytopenia caused by disease progression and immune disorders.[87]

Reversible Non-Covalent BTK Inhibitors

Orelabrutinib

Orelabrutinib, a novel highly selective small-molecule BTK inhibitor, effectively reduces off-target effects through a non-covalent binding mechanism.[88] The drug has been clinically approved for lymphoma treatment, and its research in the field of immune disease therapy is also being actively explored, such as in relapsed/refractory idiopathic multicentric Castleman disease.[89,90]

Multiple studies have confirmed that orelabrutinib demonstrates remarkable biological activity in the treatment of primary ITP. Its mechanism of action primarily involves the following aspects: First, by inhibiting the BCR signaling pathway, it effectively blocks B-cell activation, proliferation, and differentiation, thereby reducing the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. Second, it reshapes the functional phenotype of B cells by downregulating B-cell ribosome biosynthesis and mitochondrial metabolic pathways. Third, it potently suppresses Fcγ receptor-mediated downstream signaling, including key molecules such as PLCγ2 and PKC, thereby significantly reducing macrophage phagocytosis of platelets and decreasing the production of macrophage-derived pro-inflammatory factors like IFN-γ. In studies using ITP mouse models, orelabrutinib exerts therapeutic effects through multiple mechanisms, including inhibiting plasma cell differentiation, reducing anti-platelet antibody production, decreasing pro-inflammatory cytokine release, and suppressing platelet phagocytosis by hepatic and splenic macrophages. These effects ultimately lead to a significant increase in platelet counts, fully validating its efficacy in blocking antibody-mediated platelet destruction.[91]

Phase II clinical trial data demonstrate that orelabrutinib not only significantly increases platelet counts and improves clinical symptoms in patients with persistent or chronic primary ITP but also exhibits favorable safety and tolerability, highlighting its promising clinical application prospects and potential to become an important innovative drug for ITP treatment.[92]

Pirtobrutinib (LOXO-305)

Pirtobrutinib, a third-generation non-covalent BTK inhibitor, has been approved for marketing by the US FDA. Its unique mechanism of action enables it to circumvent drug resistance mediated by BTK C481 mutations, maintaining significant pharmacological activity even against BTK carrying the C481 mutation.[93] Currently, the primary indication for this drug is drug-resistant hematological malignancies, while research on its use in immune diseases such as ITP remains in the clinical trial phase.[94]

Pirtobrutinib does not form covalent bonds with the C481 site of BTK. Instead, it inhibits BTK kinase activity by reversibly binding to the ATP-binding domain of BTK. This non-covalent binding mode mechanistically blocks the resistance pathway caused by C481 site mutations, significantly reducing the risk of drug resistance.[95] Compared with traditional covalent BTK inhibitors, pirtobrutinib exhibits superior safety profiles, particularly with significantly lower incidences of adverse reactions such as bleeding events and atrial fibrillation.[96] However, due to its pharmacokinetic properties, continuous administration is required to maintain effective plasma drug concentrations, and its long-term clinical efficacy and safety still need to be further verified by large-scale, long-term follow-up studies.

In the field of hematological oncology, pirtobrutinib holds significant clinical value in the treatment of relapsed/refractory MCL. As the first BTK inhibitor to demonstrate durable therapeutic responses in heavily pretreated relapsed/refractory MCL patients who have undergone multi-line therapy and received covalent BTK inhibitors, its favorable drug tolerability and low drug-related toxicity discontinuation rate provide a safer and more effective new treatment option for this poor-prognosis patient population.[97]

Additionally, clinical research data demonstrate that pirtobrutinib also exhibits favorable safety and efficacy in the treatment of various other B-cell malignancies, such as chronic lymphocytic leukemia and small lymphocytic lymphoma, particularly in patients previously treated with covalent BTK inhibitors. This characteristic indicates that pirtobrutinib holds promise to meet the growing clinical need for novel alternative treatment regimens in such patients.[98]

Tirabrutinib (Second-Generation Reversible Inhibitor)

The latest meta-analysis results show that tirabrutinib monotherapy demonstrates manageable safety and favorable clinical efficacy in the treatment of relapsed or refractory B-cell lymphoma/leukemia.[99] Additionally, early clinical studies conducted in Japan have preliminarily confirmed that the novel BTK inhibitor tirabrutinib has therapeutic effects in some patients with primary ITP.[100] However, due to the limited sample size of this study, its clinical efficacy still requires further verification through large-sample, multicenter clinical research.

A 72-year-old male patient with refractory ITP was diagnosed with IgM-MGUS as the underlying disease after comprehensive evaluation. The patient did not achieve the expected response to bendamustine combined with rituximab, but subsequent treatment with tirabrutinib plus conventional therapy successfully restored platelet counts to normal levels. This case highlights the importance of enhancing screening and monitoring for underlying diseases in the management of refractory ITP patients. Meanwhile, given that IgM-MGUS represents an intervenable pathological state, it may serve as a potential target for precision-targeted therapy with tirabrutinib, providing new insights for the development of individualized treatment strategies in such patients.[101]

Comparison with Conventional Therapies

In the field of ITP treatment, rilzabrutinib, as a novel targeted therapy, together with traditional first-line treatment regimens, forms a diversified therapeutic landscape. Currently, first-line drugs for ITP mainly include glucocorticoids, IVIG, and TPO-RAs, with eltrombopag being a representative TPO-RA. To clearly illustrate the characteristic differences between rilzabrutinib and traditional first-line therapies, key information such as onset speed, sustained response rate, long-term side effects, and applicable populations of the four are systematically compared (see Table 2).

Glucocorticoids

Glucocorticoids, as first-line therapeutic agents for ITP, are widely used in clinical practice. Relevant studies have shown that HIF1A gene polymorphisms are not significantly associated with the susceptibility to childhood ITP, but the CT genotype at the rs11549465 locus is correlated with the sensitivity of pediatric ITP patients to glucocorticoid therapy. This suggests that single-nucleotide polymorphism at this locus may be a potential genetic factor influencing glucocorticoid treatment sensitivity in pediatric ITP patients.[102] Additionally, single-nucleotide polymorphism loci such as rs17446593, rs17446614, and rs2721068 in the FOXO1 gene are closely associated with the severity of bleeding and glucocorticoid treatment sensitivity in childhood ITP.[103]

The GR plays a core regulatory role in the pathophysiological process of ITP.[104] In MDSCs of ITP patients, GR expression levels are significantly reduced. GR can translocate to mitochondria, maintaining cellular metabolic

Table 2 Comparative Analysis of Rilzabrutinib and Traditional First-Line Therapies for ITP

Indicator	Rilzabrutinib	Glucocorticoids	IVIG	TPO-RA
Onset speed	Rapid (1–2 weeks)	Rapid (1–2 weeks)	Extremely rapid (24–72 hours)	Slow (4–6 weeks)
Sustained response rate	Relatively high (approximately 40%)	Low (prone to recurrence)	High in the short term (80%-90%), low in the long term (25%-40%)	Moderate (50–60%)
Long-term side effects	Low (no reports of hepatotoxicity yet)	High (osteoporosis, infection)	Thrombosis, hemolysis, infection risk (low probability)	Moderate (hepatotoxicity, thrombosis risk)
Target population	Refractory/relapsing ITP	Naive patients	Acute bleeding, children, pregnancy, preoperative	Chronic ITP maintenance therapy

homeostasis by regulating mtDNA transcription and oxidative phosphorylation processes. Abnormal GR expression or functional defects lead to mitochondrial physiological dysfunction and decreased gene transcription in MDSCs, accompanied by reduced expression of CPT-1, a rate-limiting enzyme in FAO. This ultimately induces aerobic metabolic disorders in cells, leading to glucocorticoid resistance. Conversely, an intact GR signaling pathway is critical for maintaining the homeostatic immunosuppressive function of MDSCs by precisely regulating their metabolic state.

In clinical practice, apart from traditional monotherapy, the treatment regimen of glucocorticoids combined with Shengxue Xiaoban Capsule has been applied in clinical intervention for ITP, providing new options for personalized therapy.[105] However, for patients with glucocorticoid-resistant primary ITP, given the limitations of conventional treatments, there is an urgent need to explore novel therapeutic strategies to improve patient outcomes.[106]

IVIG

IVIG, a first-line therapeutic agent for ITP, is prepared from human plasma and used in the treatment of AIDs.[107] In 1981, Dr. Paul Imbach first reported that high-dose IVIG promotes rapid recovery in children with ITP.[108] Through systematic monitoring of splenic index, proportion of CD16+ macrophage subsets, polarization status of M1 and M2 macrophages, and dynamic detection of cytokine levels (eg, IL-6, IL-27, IL-13), studies have confirmed significant sex-specific efficacy differences of IVIG in treating ITP.[109]

The CD4/CD8 ratio can serve as an important indicator for evaluating the efficacy of IVIG in treating children with immune thrombocytopenic purpura.[110] Related studies have shown that IVIG treatment can effectively promote the recovery of ITP children with platelet thrombin activation and abnormal thrombin generation;[111] meanwhile, clinical data confirm that platelet counts in children increase significantly after IVIG treatment.[112]

In addition to rilzabrutinib, multiple novel therapeutic products have been developed. Among them, the fragment crystallizable-modified anti-haptoglobin monoclonal antibody offers the advantage of lower dosing compared to IVIG.[35] The novel small-molecule phagocytosis inhibitor KB-208 demonstrates therapeutic efficacy comparable to IVIG.[113] Furthermore, clinical studies confirm that a novel 10% IVIG formulation for treating Chinese patients with primary ITP not only exhibits favorable therapeutic effects but also maintains high safety.[114]

TPO-RAs

TPO-RAs enhance the immunosuppressive activity of MDSCs, and this regulatory process is dependent on platelet TGF-β1.[115] A prospective multicenter study showed that in adult patients with primary ITP who discontinued TPO-RA after achieving complete remission, some patients achieved sustained treatment-free responses (platelets $\geq 30\times10^9$/L without bleeding). At 24 weeks, 30% of patients maintained the response, and at 52 weeks, 29% did so. Recurrent cases had no severe bleeding, and retreatment remained effective. $CD8^+$ T cell-related immune signatures may be associated with the persistence of treatment-free responses, supporting attempts to gradually reduce and discontinue TPO-RA in patients with stable remission.[116]

During the COVID-19 pandemic, TPO-RAs were recommended for the treatment of primary ITP. However, studies have reported that thrombocytosis and thrombosis occasionally occur in chronic ITP patients receiving TPO-RA during COVID-19 infection.[117] A US multicenter retrospective study showed that adult ITP patients switched from eltrombopag or romiplostim to avatrombopag achieved a platelet response rate of 93% and a complete response rate of 86%, with high response rates even in those with suboptimal responses to prior TPO-RA therapy, confirming the efficacy of avatrombopag in treated chronic ITP patients.[118] Another study demonstrated that ITP patients can safely transition to avatrombopag therapy, which not only maintains platelet count targets but also improves treatment satisfaction.[119]

In the UK, TPO-RAs are one of the treatment options for adult ITP.[120] The Stop TPO-Receptor Agonist in ITP Patients prospective study confirmed that after 1 year of romiplostim treatment, adult chronic ITP patients who gradually reduced the dose achieved a sustained treatment-free remission rate of 23.6% 1 year after discontinuation. The study found that patients with sustained treatment-free remission had higher platelet levels during treatment, lower starting doses for dose reduction, reduced anti-platelet antibodies in some cases, and improved platelet survival was associated with sustained remission, suggesting that a gradual dose reduction strategy with romiplostim may be attempted in selected patients.[121]

Future Directions and Challenges

Phase I studies of rilzabrutinib in healthy subjects showed no significant pharmacokinetic changes when co-administered with quinidine, but a substantial reduction in exposure when co-administered with rifampin. Monotherapy or combination with both drugs was well-tolerated. Studies confirmed that rilzabrutinib is a CYP3A substrate rather than a P-gp substrate.[122] Future research directions may explore the expanded application of rilzabrutinib in pediatric ITP and patients with comorbid autoimmune diseases (such as SLE-ITP). Additionally, its combination with FcRn inhibitors (eg, Efgartigimod) may further reduce antibody-mediated platelet destruction through synergistic mechanisms.[123] Long-term safety monitoring over 5+ years is also required to confirm the absence of delayed side effects (eg, risk of secondary malignancies).[124]

Conclusion

Currently, rilzabrutinib is the BTK inhibitor with the best overall efficacy in treating ITP, with its rapid onset of action, high safety profile, and efficacy in refractory cases having been preliminarily validated. However, long-term data from phase III clinical trials are still needed to support its recommendation as a first-line treatment. For ITP patients unresponsive to conventional therapies, participation in relevant studies under the guidance of clinicians is advisable. (The complete abbreviations are shown in the List of Abbreviations).

Abbreviations

ADCC, antibody-dependent cell-mediated cytotoxicity; Akt, protein kinase B; AIC, autoimmune cytopenia; AIDs, autoimmune diseases; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; Ca^{2+}, calcium; CDC, complement-dependent cytotoxicity; CLEC-2, C-type lectin-like receptor 2; CLL, chronic lymphocytic leukemia; CPT-1, carnitine palmitoyltransferase-1; CR, complement receptors; DAG, diacylglycerol; FAO, fatty acid oxidation; FcγR, Fcγ receptor; FDA, food and drug administration; GPIb, glycoprotein Ib; GPVI, glycoprotein VI; GR, glucocorticoid receptor; LDH, lactate dehydrogenase; LTE, long-term extension; LUNA, long-term utility and novel approach; Lyn, Lck/Yes-related novel tyrosine kinase; IC50, half-maximal inhibitory concentration; IFN-γ, interferon-γ; IgM-MGUS, immunoglobulin M monoclonal gammopathy of undetermined significance; IL, interleukin; IP3, inositol trisphosphate; ITAMs, immunoreceptor tyrosine-based activation motifs; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; MCL, mantle cell lymphoma; MDSCs, myeloid-derived suppressor cells; mtDNA, mitochondrial DNA; NETs, neutrophil extracellular traps; NF-AT, nuclear factor of activated T cells; NF-κB, nuclear factor κB; NGAL, neutrophil gelatinase-associated lipocalin; PI3K, phosphatidylinositol-3 kinase; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PKC, protein kinase C; PLCγ2, phospholipase Cγ2; SFKs, Src family kinases; SLE, systemic lupus erythematosus; Syk, spleen tyrosine kinase; TGF-β1, transforming growth factor-β1; TNF-α, tumor

necrosis factor-α; TPO-RAs, thrombopoietin receptor agonists; VITT, vaccine-induced immune thrombotic thrombocytopenia; vWF, von Willebrand factor.

Consent for Publication

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