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CASE SERIES

Combination Therapy with Romiplostim, Danazol, and a Thrombopoietin Receptor Agonist for Immune Restoration in Chronic Refractory Immune Thrombocytopenia: A Case Series

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Background: Chronic refractory primary immune thrombocytopenia is defined as thrombocytopenia refractory to multiple therapies using second-line agents with or without splenectomy. Patients face the threat of severe bleeding, and it is challenging to achieve effective treatment. Although thrombopoietin receptor agonists (TPO-RAs) and immunomodulators have been established as second-line options, their efficacy as monotherapy remains suboptimal.

Methods: Here, we report the early and durable response to a novel triple regimen combining romiplostim, danazol, and either hetrombopag or eltrombopag in two patients with chronic refractory primary immune thrombocytopenia at our center, with a follow-up exceeding 4 months.

Results: The bleeding score decreased from grade 3/4 to grade 0 during the follow-up. No significant treatment-related adverse events were observed during the follow-up.

Conclusion: Romiplostim in combination with danazol and hetrombopag or eltrombopag may be a safe and efficacious therapy for chronic refractory primary immune thrombocytopenia; however, this needs to be further explored.

Keywords: chronic refractory immune thrombocytopenia, TPO receptor agonists, romiplostim, danazol, combination therapy

Introduction

Immune thrombocytopenia (ITP) is the most common autoimmune bleeding disorder and is characterized by accelerated platelet destruction and impaired platelet production. Up to 70% of these patients experience a chronic course, and 10–30% of patients progress to refractory thrombocytopenia.[1,2] Among refractory cases, severe ITP represents a critical hematological emergency marked by profoundly low platelet counts and a high bleeding tendency, which is associated with higher morbidity and mortality rates. Therefore, rapid platelet count elevation is necessary to mitigate life-threatening hemorrhages, particularly internal bleeding and intracerebral hemorrhage.[3] However, a subset of patients with chronic severe refractory ITP remains unresponsive to multiple lines of therapy, underscoring the urgent need for novel strategies.

The introduction of thrombopoietin receptor agonists (TPO-RAs) has revolutionized ITP treatment by directly stimulating megakaryopoiesis. This class includes agents such as romiplostim, eltrombopag, hetrombopag, and avatrombopag. A key pharmacological advantage of TPO-RAs over recombinant human thrombopoietin (rhTPO) is their ability to bind to distinct sites on the TPO receptor, avoiding competition with endogenous TPO and potentially enabling

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synergistic effects.[4,5] Romiplostim, a peptibody, engages the extracellular domain, whereas non-peptide agents like eltrombopag and hetrombopag target the transmembrane domain.[6] Hetrombopag, a second-generation TPO-RA developed in China, offers structural modifications that confer high potency at low daily doses (2.5–5 mg) with a favorable hepatorenal safety profile.[7] Romiplostim uniquely activates STAT3 signaling alongside the JAK2/STAT5 pathway, which may contribute to enhanced platelet production and immunomodulation via FcγRIIb engagement.[8] The rational combination of TPO-RAs with complementary binding sites presents a promising approach to overcome receptor saturation or clinical resistance, a concept supported by studies showing efficacy upon switching between agents.[9,10]

Beyond stimulating platelet production, addressing the underlying immune dysregulation is critical. Danazol, a synthetic androgen with established immunomodulatory properties, complements the action of TPO-RAs. It is thought to correct CD4+/CD8+ T-cell imbalances, suppress pro-inflammatory cytokines, and reduce Fc receptor-mediated phagocytosis of platelets.[11]

Herein, we present two cases of chronic severe refractory ITP with a high bleeding risk that achieved complete remission after triple therapy with romiplostim (a TPO-RA), danazol, and either hetrombopag or eltrombopag, which are also TPO-RAs. This report aimed to provide insights into the clinical management of similar challenging cases.

Treatment Protocol and Assessment

Given the severe and refractory nature of the ITP in these cases, a standardized yet individualized treatment protocol was followed for the triple-combination therapy.

Treatment Regimen

The combination therapy consisted of:

1) Romiplostim: Administered subcutaneously at a starting dose of 3–5 μg/kg once weekly.
2) Danazol: Administered orally at 200 mg twice daily.
3) A second TPO-RA: Either hetrombopag (5 mg orally once daily) or eltrombopag (50 mg orally once daily).

Dose Titration and Monitoring

Dose adjustments were made based on weekly complete blood count (CBC) measurements. The goal was to achieve and maintain a platelet count $\geq 50\times10^9$/L to mitigate bleeding risk while avoiding thrombocytosis ($>400\times10^9$/L).

1) Romiplostim: The dose was titrated in increments of 1–2 μg/kg per week if the platelet response was suboptimal ($<50\times10^9$/L). The dose was reduced or temporarily held if the platelet count rose excessively.
2) Hetrombopag/eltrombopag: The daily dose was maintained or adjusted according to the platelet response and the manufacturer's guidelines.
3) Danazol: The dose was maintained at 400 mg daily, with close monitoring of liver function tests.

Follow-Up

Patients were followed weekly for the first month to monitor the initial response and adjust doses. Upon stabilization of platelet counts, the follow-up interval was extended to every 2–4 weeks. Each follow-up included a clinical assessment for bleeding symptoms and treatment-related adverse events, a CBC, and periodic biochemical profiling to monitor liver and renal function.

Response Criteria

Treatment response was defined according to the standardized criteria from the International Consensus Report (ICR):[12]

Complete Response (CR): A platelet count $\geq100\times10^9$/L in the absence of bleeding.

Response (R): Platelet count between 30 and 100×10^9/L with at least a doubling from baseline in the absence of bleeding.

No Response (NR): Platelet count $<30\times10^9$/L or less than a doubling from baseline.

Relapse: Loss of CR or R after initial achievement.

Case 1

A 54-year-old man was admitted to our center on September 12, 2017, because of cutaneous and mucosal bleeding (Table 1). The patient had a 10-year history of hypertension and maintained a well-controlled blood pressure with regular levamlodipine besylate therapy. Physical examination was negative, except for large bruises and petechiae over the lower extremities and buccal mucosa. Blood counts and confirmatory blood smear revealed the following: platelet count 4×10^9/L, hemoglobin 130 g/L, and white blood cell (WBC) count 5.28×10^9/L. Routine blood coagulation tests were normal. No significant abnormalities were detected in thyroid function, lupus anticoagulant, β2-glycoprotein 1 antibodies, antinuclear antibody, human immunodeficiency virus testing, and anticardiolipin antibodies. Immunoglobulin levels were within the normal range. Serological testing excluded a viral hepatitis etiology, with negative results for hepatitis B surface antigen, anti-HBc IgM, and anti-HCV antibodies. The patient was diagnosed with severe primary ITP with a bleeding symptom score of 3. The patient was treated with 1 week of corticosteroid therapy (intravenous methylprednisolone, 60 mg), and his platelet count returned to normal.

On August 25, 2023, the patient presented with a platelet count of 10×10^9/L, generalized mucocutaneous bleeding, and recurrent epistaxis. Methylprednisolone and thrombopoietin (TPO, 300 μg/kg daily) were added to his treatment regimen, resulting in an increase in platelet count to 84×10^9/L. On September 30, 2023, the patient was again admitted because of cutaneous and mucosal bleeding, as well as subconjunctival hemorrhage, with the platelet count dropping to $0x10^9$/L. Despite subsequent treatment with multiple courses of corticosteroids, intravenous immunoglobulin (IVIG), rituximab, TPO, and blood transfusion, a significant or sustainable response was not achieved.

On May 13, 2024, the patient's platelet count was 0×10^9/L. A specific antiplatelet antibody panel was positive for glycoprotein IIb and GMP140. Bone marrow cytology revealed active proliferation, characterized by maturation disorders in the megakaryocytic lineage and sparse platelet production (55 granular megakaryocytes and 3 platelet-producing megakaryocytes, with poor platelet production). Flow cytometric analysis of the bone marrow revealed no significant abnormalities. A bone marrow biopsy demonstrated no evidence of immature cells or increased lymphocytes, and no dysplastic features were observed in the megakaryocytes (normal megakaryocyte count with predominantly lobulated nuclei). Despite treatment with high-dose corticosteroids, IVIG, and platelet infusions, the patient's platelet count remained low. Hetrombopag (5 mg daily for 2 weeks) was added to the regimen; however, the patient continued to experience epistaxis, with a platelet count of 10×10^9/L. Romiplostim (3 μg/kg weekly) and danazol (0.2 g twice daily) were added to the treatment regimen, along with continued treatment with hetrombopag. Remarkably, within 8 days of the treatment, his platelet count began to progressively increase, with a platelet count of 141×10^9/L on June 21, 2024, and a platelet count of 324×10^9/L on June 23, 2024. The immunological profiles before and after triple therapy are shown in Table 2. Prior to treatment, the patient exhibited significantly reduced absolute counts of $CD4^+$ and $CD8^+$ T cells, along with T cell activation, an increased proportion of regulatory T cells (Tregs), and elevated tumor necrosis factor (TNF) levels. Following therapy, as the platelet count increased, $CD4^+$ and $CD8^+$ T cell counts increased, T cell activation diminished, and the proportion of Treg cells decreased. Concurrently, TNF levels returned to normal, signifying progressive restoration of immune homeostasis.

During routine follow-up, the platelet count remained above 50×10^9/L for 4 months. Hetrombopag was gradually tapered, and the dose of romiplostim was reduced to 1 μg/kg weekly. The patient did not experience any significant

Table 1 Patient Characteristics

	Age (Years)	Sex	Year of ITP Diagnosis	Time from Diagnosis to Start of Triple Therapy (Months)	Previous ITP Treatments	Baseline WBC count ($\times10^9$/L)	Baseline Hb (g/L)	Baseline Platelets ($\times10^9$/L)
Patient 1	54	Man	2017	80	Glucocorticoid; TPO; IVIG; rituximab; hetrombopag	5.28	130	4
Patient 2	26	Woman	2021	38	Glucocorticoid; TPO; IVIG; eltrombopag	6.94	126	2

Abbreviations: TPO, thrombopoietin; IVIG, intravenous immunoglobulin; WBC, white blood cell; Hb, hemoglobin.

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Table 2 Immunological Profiling Before and After Triple Therapy in Two Patients with Severe Refractory ITP

Parameter	Patient 1		Patient 2		Normal Range
	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment	
$CD4^+$ T cells (cells/μL)	155	288	481	743	331–1293
$CD8^+$ T cells (cells/μL)	215	229	522	535	228–941
$CD4^+/CD8^+$ ratio	0.72	1.26	0.92	1.39	1.3–2.6
Activated $CD3^+HLA\text{-}DR^+$ (%)	23	10	9.7	5.0	1.8–4.4
Treg cells (%)	16.42	8.5	5.63	4.17	5–10
Serum TNF-α (pg/mL)	10.5	8.1	12.3	7.9	<8.1

Abbreviations: Tregs, regulatory T cells; TNF, tumor necrosis factor.

adverse reactions during the treatment. The changes in platelet counts and types of intervention are shown in Figure 1. A concise chronological timeline of key clinical events, including diagnosis, major treatments, and outcomes for patient in Figure 2.

Case 2

A 26-year-old woman presented to our medical center in June 2021 with generalized mucocutaneous bleeding and recurrent epistaxis. The patient had no significant medical history. Physical examination was negative except for petechiae and ecchymoses on the abdomen and extremities. An abnormal CBC was found during a routine check-up: platelet count 2×10^9/L, hemoglobin 126 g/L, WBC count 6.94×10^9/L. The blood smear was remarkable only for the decreased number of platelets. Evaluations indicated that she was negative for antinuclear antibodies, anticardiolipin antibodies, antineutrophil cytoplasmic antibody spectrum, and lupus anticoagulant. Bone marrow cytology revealed a reduced platelet count (no megakaryocytes were observed throughout the slide, and platelets were sparsely distributed). A bone marrow biopsy revealed hyperplasia of the granulocytic and erythroid lineages with visible megakaryocytes. She

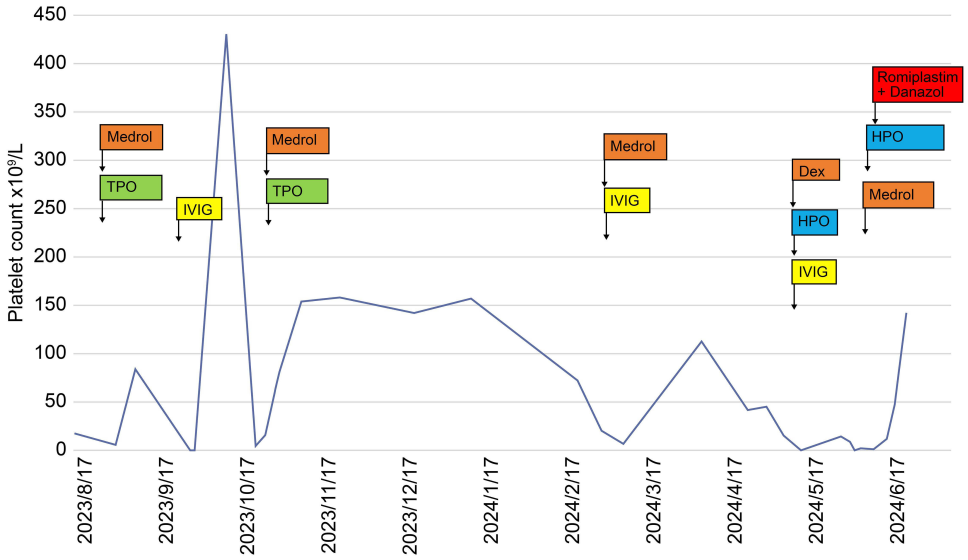

Figure 1 Patient 1: temporal changes in platelet count and types of intervention.
Abbreviations: Medrol, methylprednisolone; TPO, thrombopoietin; IVIG, intravenous immunoglobulin; Dex, dexamethasone; HPO, hetrombopag.

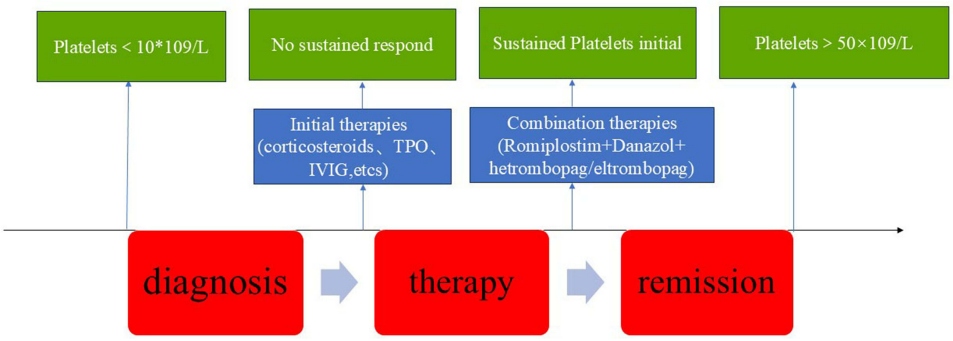

Figure 2 A concise chronological timeline of key clinical events, including diagnosis, major treatments, and outcomes for both patients.

was diagnosed with severe ITP, with a bleeding symptom score of 4, and was treated with methylprednisolone (80 mg daily) for 1 week, without achieving a significant or sustainable response. TPO (300 μg/kg daily) was then added to the treatment regimen for 1 week, after which the platelet count returned to normal. The patient was further treated with oral corticosteroids, which were gradually tapered. During repeated follow-up assessments, the patient's platelet count remained at >30×10^9/L.

On April 23, 2024, the patient, at 37+2 weeks of gestation, was readmitted with gingival bleeding and purpura on her extremities, and a decreased platelet count of $1x10^9$/L. She was administered two apheresis units of platelets for active bleeding, dexamethasone (10 mg daily), and IVIG (400 mg/kg on days 1–4), and underwent an emergency cesarean delivery. In the first month after admission, her platelet count ranged from 1 to 8×10^9/L despite treatment with corticosteroids and IVIG. TPO (300 μg/kg daily) was subsequently administered, with platelet counts being maintained between 30–50×10^9/L over the following 2-month period. During her hospital stay, evaluations indicated she was positive for anti-GPIX antibodies, anti-GPIIIa antibodies, and anti-GMP-140 antibodies.

On July 18, 2024, the patient experienced epistaxis and vaginal bleeding, and the platelet count decreased to 6×10^9/L. Treatments with methylprednisolone, IVIG, or TPO were ineffective. Eltrombopag (50 mg once daily) was initiated as adjunctive therapy for 10 consecutive days, but failed to achieve a clinically meaningful hematologic response (platelet count <30×10^9/L throughout treatment). Romiplostim (3 μg/kg weekly) and danazol (200 mg bid) were initiated on August 1, 2024, as combination therapy with ongoing eltrombopag. Eleven days after treatment initiation, the platelet count had increased to 118×10^9/L. Longitudinal immunological profiling revealed immune reconstitution (Table 2).

The patient tolerated romiplostim and danazol well, without transaminitis or other toxicities. During treatment, the patient complained of insomnia, weight gain, and dysphoria on corticosteroids, with multiple purple striae distributed diffusely over the body surface. Therefore, corticosteroids were tapered off. Throughout the 4-month follow-up period, platelet counts consistently remained above 50×10^9/L. Consequently, eltrombopag was discontinued, whereas romiplostim dosage was gradually tapered to a maintenance regimen of 1 μg/kg administered weekly. The changes in platelet counts after treatment are shown in Figure 3. A concise chronological timeline of key clinical events, including diagnosis, major treatments, and outcomes for patient in Figure 2.

Discussion

ITP is a complex, heterogeneous disorder characterized by various clinical manifestations. Patients may present with asymptomatic thrombocytopenia, skin and mucous membrane bleeding, severe visceral bleeding, or even fatal intracranial hemorrhage.[13] First-line therapies, such as corticosteroids, remain the cornerstone of initial management, but a significant proportion of patients develop steroid resistance or dependency. Second-line options, including rhTPO, rituximab, romiplostim, eltrombopag, and splenectomy, have demonstrated variable efficacy and have limitations. Notably, 70–80% of patients fail to sustain platelet counts post-therapy, progressing to chronic refractory severe ITP, a hematological emergency requiring rapid platelet elevation to mitigate catastrophic bleeding and mortality. However,

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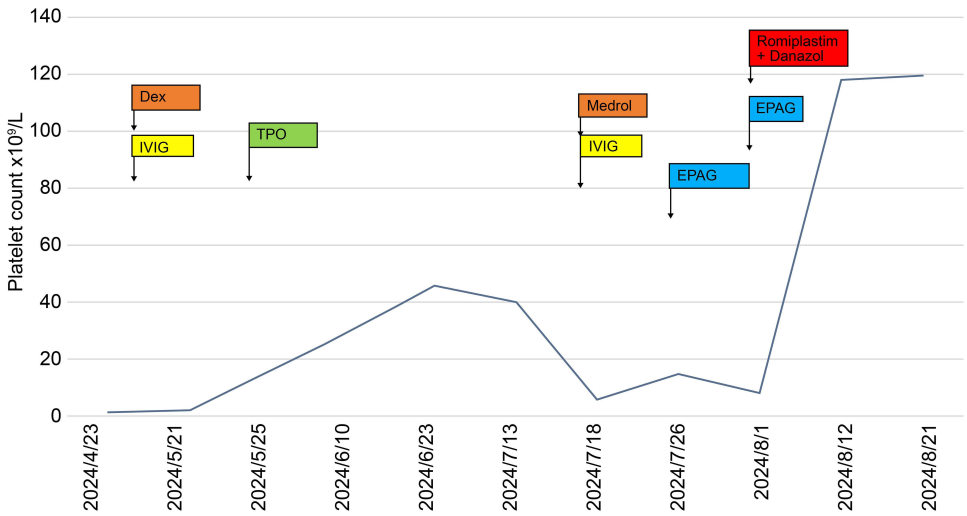

Figure 3 Patient 2: temporal changes in platelet count and types of intervention.
Abbreviations: Medrol, methylprednisolone; TPO, thrombopoietin; IVIG, intravenous immunoglobulin; Dex, dexamethasone; HPO, hetrombopag.

standardized guidelines for managing chronic refractory severe ITP are lacking, reflecting the challenges in therapeutic optimization and the absence of robust randomized trials to inform treatment sequencing.[14] Advances in novel agents and combination strategies have shifted ITP management from conventional immunosuppression toward personalized, multi-targeted approaches. Therefore, individualized and stratified treatments are essential for the management of severe adult refractory ITP.

Over the decades of research, ITP has been recognized as a multifaceted process involving dysregulated interactions between immune effector cells and inflammatory mediators. Current therapeutic strategies primarily target two axes: (1) attenuating immune-mediated platelet destruction through immunosuppressive agents (eg, corticosteroids, IVIG, rituximab, or splenectomy) and (2) enhancing platelet production via TPO analogs, including rhTPO and TPO-RAs.[15] First-line therapies such as corticosteroids and IVIG achieve transient responses in approximately two-thirds of patients, whereas one-third exhibit primary resistance or relapse upon dose reduction/discontinuation. Second-line options, including rituximab, romiplostim, eltrombopag, and splenectomy, demonstrate partial efficacy with limitations in terms of sustained response. Although rhTPO demonstrates rapid efficacy, its cross-reactivity with endogenous TPO and the potential for tachyphylaxis limit its long-term utility.[16]

Danazol demonstrated favorable long-term remission rates in older patients with ITP. A cohort study of 96 patients (36 men and 60 women) reported an overall response rate (ORR) of 61.4%, with enhanced efficacy observed in non-splenectomized older women, positioning danazol as a viable alternative to splenectomy in this population. A multicenter, randomized, open-label Phase II trial that evaluated 93 adults with steroid-resistant or relapsed ITP found that the 12-month sustained response rate was significantly higher in the all-*trans* retinoic acid plus danazol group than in the danazol monotherapy group (62% vs 25%, respectively). A meta-analysis of immunomodulatory agents for chronic ITP corroborated these findings, reporting an aggregate ORR of 58% for danazol, which surpassed that of many conventional immunosuppressants.[17]

Conventional therapies for ITP often yield suboptimal outcomes with limited durable remission rates and cumulative toxicity risks from prolonged monotherapy. To address these limitations, combination strategies targeting multiple pathological axes, such as platelet destruction and production, have emerged as promising approaches. The rationale lies in leveraging additive or synergistic effects through distinct mechanisms: TPO-RAs enhance megakaryopoiesis, whereas immunomodulators mitigate immune-mediated platelet clearance. A French multicenter retrospective study[18] involving 37 patients with refractory ITP demonstrated the superior efficacy of TPO-RA (eltrombopag/romiplostim) combined with immunosuppressants (mycophenolate mofetil, hydroxychloroquine, or cyclophosphamide) versus monotherapy. The combination therapy group achieved a 70% response rate (vs 7.1% with monotherapy) and a median

response duration of 15 months. Updated 2023 data revealed further improvement, with a 77% platelet response rate and 63% sustained remission.[19] Similarly, a retrospective study by Gudbrandsdottir et al[20] reported a 72.2% response rate in 18 refractory patients treated with TPO-RAs, cyclosporine/mycophenolate, and IVIG. Notably, responders exhibited reduced TPO-RA dosing (six patients), IVIG independence (five patients), and romiplostim discontinuation (one patient), with no severe adverse events. Remarkably, combining TPO-RAs with danazol, a strategy targeting thrombopoiesis and immune dysregulation, achieved 100% efficacy in 16 eltrombopag-refractory patients compared to 75% with romiplostim monotherapy.[21] These findings underscore the potential of TPO-RA-danazol regimens to synergistically suppress platelet destruction while stimulating production, offering a viable strategy for chronic severe refractory ITP. Our cases further validate this approach: two patients with chronic refractory severe ITP with profound thrombocytopenia ($<10\times10^9$/L) and high bleeding risk achieved complete remission following triple therapy with romiplostim + danazol + hetrombopag/eltrombopag. Longitudinal immune profiling revealed pre-treatment T-cell dysregulation (reduced $CD4^+/CD8^+$ counts, elevated activated T-cells/Tregs, and TNF-α hyperexpression), which normalized post-treatment, reflecting restored immune homeostasis. The striking clinical and immunological response observed in our two patients with severe refractory ITP raises the possibility of synergistic mechanisms underlying the romiplostim–danazol–hetrombopag/eltrombopag regimen. To our knowledge, this is the first report to describe the use of this specific triple combination. Although the precise mechanism remains unclear, we propose a model of complementary action. First, the two TPO-RAs, by binding to distinct domains of the TPO receptor (romiplostim to the extracellular domain and hetrombopag/eltrombopag to the transmembrane domain),[22,23] may provide a synergistic stimulus for megakaryocyte proliferation and platelet production. This "dual agonist" approach could maximize intracellular JAK2/STAT signaling, promoting a more rapid and sustained platelet increase than either agent alone, thereby reducing bleeding risk and supporting endothelial integrity. Second, danazol, a synthetic androgen, is thought to exert immunomodulatory effects beyond its modest thrombopoietic activity. It may downregulate Fcγ receptor expression on splenic macrophages, reducing platelet destruction,[24] while also correcting Th1/Th2 imbalance and modulating Treg function in ITP,[25] thus targeting the underlying immune dysregulation. We hypothesize that therapeutic synergy arises from this "dual-pathway" approach: the TPO-RA combination provides immediate platelet support by enhancing production, whereas danazol concurrently attenuates immune-mediated platelet destruction. This integrated mechanism may interrupt the cycle of severe refractory ITP more effectively than sequential or single-agent therapy. However, this study has some limitations. The small sample size (two cases) restricts generalizability, and as a case series, the observations are associative rather than causal. The proposed mechanistic synergy is speculative, inferred from pharmacology of the individual agents rather than direct experimental evidence. Future in vitro studies and larger prospective clinical trials are needed to validate these hypotheses and to establish the optimal dosing strategy and long-term safety profile of this regimen.

Conclusion

This report highlights the potential of combining romiplostim, danazol, and either hetrombopag or eltrombopag to achieve rapid platelet recovery, reduce bleeding risk, and induce durable remission in refractory ITP. However, clinical evidence supporting multidrug combinations remains limited, highlighting the need for further comparative studies to refine individualized regimens. Future research should also focus on elucidating the underlying synergistic mechanisms and assessing the long-term safety of this approach.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University. Institutional approval was granted for the publication of case details by The First Affiliated Hospital of Nanchang University. Written informed consent was obtained from all patients.

Consent for Publication

Written informed consent for publication was obtained from all patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article was submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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