Cancer Pathogenesis and Therapy 1 (2023) 154–156

Contents lists available at ScienceDirect

Cancer Pathogenesis and Therapy

journal homepage: www.journals.elsevier.com/cancer-pathogenesis-and-therapy

Case report

# Combination of two target agonists of the thrombopoietin and thrombopoietin receptor in the treatment of elderly patients with refractory immune thrombocytopenia

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## HIGHLIGHTS

- Combined use of a single thrombopoietin receptor (TPO-MPL) signaling pathway with different agonists is safe with rapid and long-lasting effects in the treatment of refractory and relapsed immune thrombocytopenia (ITP).
- Dual targets agonist in the single TPO-MPL signaling pathway therapy is safe in over-aged ITP patients.
- Oral TPO-receptor agonist (RA) alone continued to maintain platelet levels after treatment with dual TPO-MPL signaling agonists.

## ARTICLE INFO

Managing Editor: Peng Lyu

*Keywords:*
Immune thrombocytopenia (ITP)
TPO-MPL signaling Pathway
rh-TPO
Eltrombopag

## ABSTRACT

Immune thrombocytopenia (ITP) is common in the elderly. Because of the coexistence of multiple diseases, there are many reservations regarding corticosteroid use in the elderly. Thrombopoietin (TPO) and its analogs can promote platelet production, but it is often difficult to correct TP in a short period. Recombinant human TPO (rh-TPO) acting on the cell membrane and the small-molecule TPO-receptor (MPL) agonist acting on the transmembrane receptor may have synergistic effects and accelerate platelet production because of different sites of action in the signaling pathway. In this study, two elderly patients with refractory ITP were successfully treated with two TPO-MPL signaling pathway agonists: recombinant human thrombopoietin (rh-TPO) and eltrombopag. This combination is safe with rapid and lasting effects. However, in elderly patients with refractory, recurrent, and glucocorticoid contraindications, the combination of different TPO agonists' clinical efficacy and adverse reactions needs to be further evaluated.

## Introduction

Glucocorticoid administration and splenectomy have been commonly used to treat immune thrombocytopenia (ITP). However, there are many reservations regarding the use of these treatment methods in the elderly.[1] In recent years, thrombopoietin (TPO) and TPO receptor (MPL) signaling pathway agonists, such as recombinant human TPO (rh-TPO) and eltrombopag, have shown good efficacy in common ITP cases. However, in refractory ITP cases, using a certain drug alone has no good outcome.[2] Based on the partial binding of these two drugs to the transmembrane and extracellular domains of the TPO receptor, we hypothesized that they might have synergistic effects in the time window and mechanism of action to accelerate platelet production. This study reviewed the clinical data and laboratory characteristics of two elderly patients with refractory ITP who were successfully treated with a combined regimen (rh-TPO and Eltrombopag). We present the following data per the Case Report (CARE) Reporting Checklist.

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https://doi.org/10.1016/j.cpt.2022.09.005
Received 18 July 2022; Received in revised form 16 September 2022; Accepted 28 September 2022

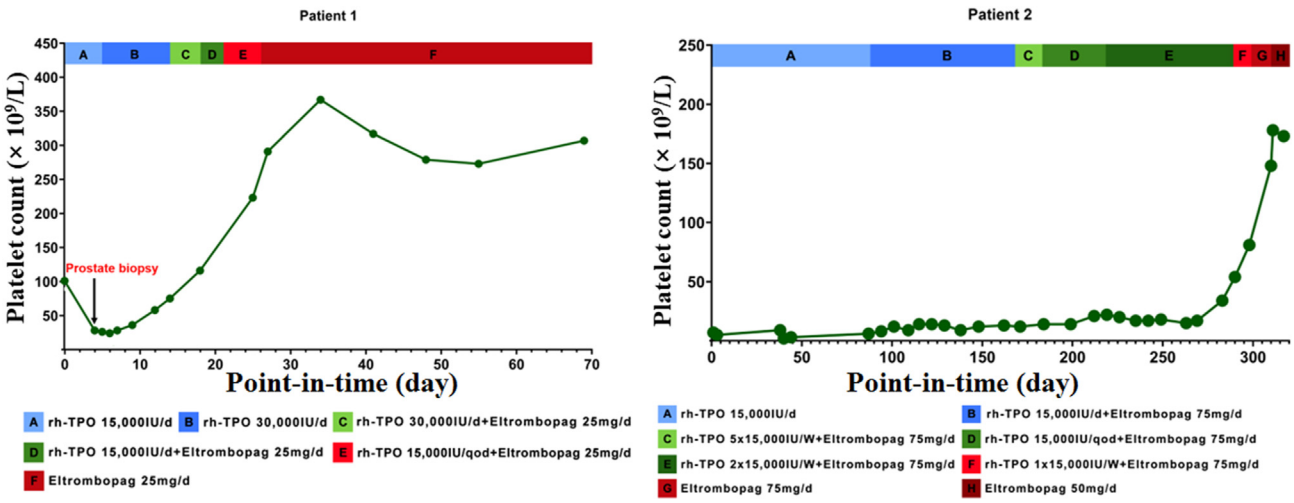


**Figure 1.** Treatment plan and corresponding peripheral blood platelet counts of two patients. rh-TPO: Recombinant human thrombopoietin.

## Case presentation

The first patient was a 76-year-old man. TP was detected on physical examination 5 years before, and the platelet count was 81 × $10^9$/L. ITP was diagnosed based on bone marrow aspiration. Amifostine was given according to a "5-day regimen" (0.4 g/day, for 5 days every week, for 6 weeks), combined with low-dose dexamethasone (2 mg/day for 4 weeks, 2 mg/every other day for 2 weeks), rh-TPO (15,000 IU/day for 8 days), and human immunoglobulin. Since then, the disease has recurred many times. After the previously mentioned treatment, the platelet count fluctuated between 52 × $10^9$/Land 130 × $10^9$/L.

The patient was hospitalized for prostate biopsy under B-ultrasound (B-US) guidance. To prevent stress TP, rh-TPO 15,000 IU/day was administered in advance. One day postoperatively, the patient showed obvious TP and was continued on treatment with rh-TPO 15,000IU/day, but the effect was unsatisfactory. On the second postoperative day, the platelet count was 14 × $10^9$/L, and rh-TPO was adjusted to 30,000 IU/day. An amifostine combined regimen and intravenous platelet transfusion were administered. After 11 days of treatment, the patient's platelet count was 63 × $10^9$/L. Eltrombopag (25 mg) was added at this time, and the patient's platelet count reached normal levels after 5 days. After the rh-TPO dose was adjusted to 15,000 IU/day for 4 days, it was further adjusted to 15,000 IU/every other day; eltrombopag was adjusted to 50 mg/day. The platelet count in the patient who gradually stopped rh-TPO but continued to take eltrombopag continued to increase and remained in the normal range, with a peak of 355 × $10^9$/L [Figure 1, left]. No obvious adverse reactions were observed during the treatment.

The second patient was an 81-year-old man who had been diagnosed with ITP 3 years before. Platelets fluctuated within the range of 60–95 × $10^9$/L. Approximately 1.5 years later, peripheral blood platelets in the patient decreased continuously, and there were many new bleeding spots in both lower limbs. In the previous 8 months, the patient had used glucocorticoids, human immunoglobulin, rh-TPO (15,000–30,000 IU), eltrombopag (50–75 mg), cyclosporine, and danazol, which had no obvious effects. During the treatment period, multiple platelet transfusions were used for symptomatic relief. Subsequently, the regimen was changed to rh-TPO 15,000 IU/day + eltrombopag 75 mg/day, and the platelet count increased gradually. Over the next 7 months, rh-TPO was decreased gradually from 15,000 IU/day to 15,000 IU/week and stopped when the platelet count reached 81 × $10^9$ IU/L. After discontinuation, the platelet count further increased, reaching the highest level of 178 × $10^9$/L. Subsequently, the amount of eltrombopag was reduced to 50 mg/day, and the platelet count remained within the normal range [Figure 1, right]. During treatment, liver and kidney functions were continuously monitored, and no obvious abnormalities were found.

## Discussion

We report the clinical data and laboratory characteristics of two elderly patients with refractory ITP. They were successfully treated with a TPO-MPL signaling pathway two-target agonist combination regimen (rh-TPO + eltrombopag). To the best of our knowledge, this is a rare study of successful refractory ITP treatment in the elderly with the TPO-receptor agonist (RA) regimen.

Traditionally, the goal of first-line ITP therapy is to rapidly increase the platelet count, which is not a priority for the persistence of drug response, long-term safety, and tolerance. Therefore, most refractory/recurrent ITP cases receive a single or repeated first-line treatment. However, studies have shown that rh-TPO plus eltrombopag is an effective and safe treatment for corticosteroid-resistant or relapsed ITP.[3]

TPO is an important megakaryocyte proliferation, differentiation, maturation, and thrombogenesis regulator. The successful application of rh-TPO and TPO-RA agonists in patients with chronic ITP and/or ineffective immunosuppressive therapeutics confirms the role of TPO and its receptors in ITP pathogenesis.[4,5]

Rh-TPO, a full-length glycosylated TPO that binds to the extracellular binding domain of the TPO receptor, takes approximately 7–9 days to take effect.[6] A multicenter, open, one-arm trial in China included 91 patients with ITP.[7] After 4 weeks of maintenance treatment with rh-TPO, the efficacy rate was 92.6%. However, Patient one in the study showed a continuous decrease in platelet count after preoperative use of rh-TPO, indicating that administering rh-TPO alone to patients who are sensitive to stress events may not rapidly increase the platelet count.

Unlike rh-TPO, eltrombopag is a synthetic low-molecular-weight oral TPO-RA that acts on the TPO receptor's transmembrane binding domain. It can stimulate platelet production at the hematopoietic stem cell level for approximately 9–14 days, with prolonged effects. After binding to the TPO receptor, eltrombopag stimulates megakaryocyte formation through the Janus kinase/signal transduction and activator of transcription (JAK/STAT) signaling pathway.[8] Unlike rh-TPO, which induces platelet neutralization antibodies, *in vitro* and *in vivo* studies of healthy volunteers and patients with ITP patients administered eltrombopag have shown that this drug does not produce neutralizing antibodies and does not affect agonist-induced platelet aggregation or activation.[9] A phase II clinical trial of relapsed/refractory patients showed that 80% of complete remission (CR) cases received eltrombopag at 50/75 mg/day. The response rate of patients to the drug was dose-dependent, and the platelet

count returned to the baseline level after 2 weeks of drug withdrawal.[10] Regarding adverse reactions, the most common side effects of Eltrombopag were headache, nausea, and liver injury. Studies have shown that the incidence of liver injury is highest in the first year of treatment, with grade 4 adverse events in the liver reaching 15%.[11] While using the combined regimen, except for a transient increase in liver function index, there were no obvious adverse reactions in the two patients, suggesting that the combined rh-TPO and eltrombopag use may have the effect of reducing the side effects. However, its specific mechanism remains to be further elucidated.

In conclusion, we reviewed the clinical data and laboratory characteristics of two elderly patients with refractory ITP who were successfully treated with a combined regimen (rh-TPO and Eltrombopag). Additionally, the combined use of both drugs further shortened the effective drug time, reduced the risk of bleeding and the occurrence of adverse reactions, and further improved the refractory ITP treatment efficacy in the elderly.

## Funding

This study was supported by the National Key Research and Development Program of China (No. 2020YFC2002706) and the Army Health Care Special Project (No. 19BJZ28).

## Author contributions

Jundong Zhang analyzed the results and wrote the manuscript. Haoran Chen and Zining Wang conducted laboratory analysis and data transcription. Xuechun Lu supervised the work and reviewed the results and the manuscript.

## Ethics statement

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 *Declaration of Helsinki* and its later amendments or comparable ethical standards. Written informed consent for publication of their details was obtained from all patients.

## Data availability statement

The data used in the current study are available from the corresponding author on reasonable request.

## Conflicts of interest

None.

## Acknowledgments

We thank the patients and their families for the publication of this study.

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