Real World Long Term TPO-RA: Sustaining Remission or Time to Stop?

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Immune thrombocytopenia (ITP) is an autoimmune disorder characterised by immune-mediated platelet destruction and impaired platelet production. Thrombopoietin receptor agonists (TPO-RAs), including **romiplostim**, **eltrombopag**, and **avatrombopag**, stimulate megakaryocyte proliferation through activation of the thrombopoietin receptor (c-MPL). These agents are widely used as second-line therapies for persistent or chronic ITP and have significantly improved disease management. Although TPO-RAs were originally considered to require continuous administration to maintain platelet counts, accumulating evidence indicates that a subset of patients can achieve **sustained response off treatment (SROT)** after therapy discontinuation.

Early randomized trials established the efficacy of TPO-RAs during active treatment. Phase III studies of eltrombopag, romiplostim and avatrombopag have demonstrated good initial responses to treatment, as well as durable platelet responses in patients with chronic ITP. While these trials primarily evaluated treatment efficacy during therapy, they also suggested that prolonged platelet recovery may influence underlying immune mechanisms.

Subsequent observational studies identified that a proportion of patients maintain adequate platelet counts after discontinuing TPO-RA therapy. Across multiple cohorts, **approximately 10–30% of patients achieve treatment-free remission**, suggesting that these agents may have disease-modifying potential beyond their thrombopoietic effect. Evidence supporting this phenomenon has been observed across different TPO-RAs, implying that sustained remission may represent a **class effect**.

Prospective evidence supporting treatment-free remission is provided by the **TAPER trial**, a phase II study evaluating eltrombopag in patients with ITP who relapsed after corticosteroid therapy. Among 105 participants, **30.5% achieved sustained response off treatment at 12 months** following gradual tapering and discontinuation of eltrombopag. Patients who achieved SROT maintained remission for a median duration of approximately 22 months, suggesting that early use of TPO-RAs may increase the likelihood of durable remission.

Real-world evidence has also been provided by the UK multicentre **TRAIT study**, which evaluated outcomes in 267 adults with ITP treated with romiplostim or eltrombopag. In this cohort, **18% of patients achieved treatment-free response** after discontinuation, defined as maintaining platelet counts ≥30 $\times 10^9$/L without further therapy. Factors associated with successful discontinuation included earlier TPO-RA initiation, use in secondary ITP, and absence of previous splenectomy.

Evidence for romiplostim-associated remission has also been reported in retrospective cohort studies. In one long-term analysis, approximately **28% of patients treated with romiplostim were able to discontinue therapy while maintaining remission**, particularly following gradual dose tapering. These findings suggest that sustained platelet recovery may contribute to restoration of immune tolerance in some individuals.

Data for avatrombopag remain limited due to its more recent introduction into clinical practice. Randomized trials have demonstrated platelet response rates comparable to those observed with romiplostim and eltrombopag; however, prospective studies specifically evaluating SROT with

avatrombopag are still lacking. Nevertheless, given its shared mechanism of thrombopoietin receptor stimulation, it is plausible that similar remission rates may be observed.

Reported SROT Rates with TPO-RAs

TPO-RA	Key Evidence	Reported SROT Rate
Romiplostim	Long-term cohort studies	~10–28%
Eltrombopag	TAPER trial and observational cohorts	~20–30%
Avatrombopag	Limited data; extrapolated from class effect	Unknown

Several immunological mechanisms have been proposed to explain sustained remission after TPO-RA therapy. These include increased regulatory T-cell activity, reduced autoreactive B-cell responses, and improved megakaryocyte function. Sustained platelet recovery may also reduce antigen presentation and inflammatory signalling, allowing restoration of immune homeostasis.

However, important limitations remain. Many studies evaluating SROT are observational and involve heterogeneous patient populations, varying definitions of remission, and differing tapering strategies. Additionally, follow-up durations vary considerably, making it difficult to determine the long-term durability of treatment-free responses. Current guidelines from the **American Society of Hematology** recognise TPO-RAs as key second-line therapies but do not yet provide formal recommendations for routine discontinuation due to limited high-quality evidence.

In conclusion, thrombopoietin receptor agonists have transformed the treatment landscape for ITP and may induce sustained remission in a subset of patients. Real life and prospective trials suggest that **approximately 15–30% of patients may achieve sustained response off treatment**. Future research should focus on identifying predictors of successful discontinuation and establishing standardized tapering protocols, particularly for newer agents such as avatrombopag.

Key References

- Cooper N et al. TAPER trial: sustained response off treatment with eltrombopag. *Am J Hematol.* 2024.
- Cooper N et al. TRAIT study: real-world outcomes of thrombopoietin receptor agonists. *Br J Haematol.* 2024.
- Cheng G et al. RAISE trial: eltrombopag in chronic immune thrombocytopenia. *Lancet.* 2011.
- Saleh MN et al. EXTEND study: long-term eltrombopag therapy. *Blood.*
- Kuter DJ et al. Romiplostim for chronic immune thrombocytopenia. *N Engl J Med.* 2008.