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The 'Stop TPO-RA in ITP Patients' study: Clinical and immune modulatory effects of romiplostim tapering

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Summary

Sustained remissions off-treatment (SROTs) after tapering of thrombopoietin receptor agonists (TPO-RAs) have been reported in 15%–50% of patients with immune thrombocytopenia (ITP). The STIP (Stop TPO-Receptor Agonist in ITP Patients) study is a prospective trial aimed to investigate the clinical effects of romiplostim tapering. Adult patients (22/40) with ITP ≥3 months received romiplostim for 1 year, were tapered and followed for 1 year. Anti-platelet antibodies (APAs), TPO levels and indium-111 platelet scintigraphy were assessed before, during and after romiplostim. Censored survival analysis showed that the probability of SROT at 1 year after tapering was 23.6% (95% confidence interval: 11.0%–50.5%). Patients with SROT had higher platelet levels on romiplostim (median: 332.5 vs. 84.5×10^9/L) and lower romiplostim doses at the start of tapering (median: 1.0 vs. 4.5 μg/kg) compared to those with a non-sustained response (NSR). APAs were detected in 8/25 patients at baseline, of which 5 showed a substantial decrease during romiplostim. The indium-111 scan revealed an improved platelet survival at the start of tapering for 50% of patients with SROT (2/4, missing $n = 1$) versus none with an NSR (0/14, missing $n = 3$). Overall, the STIP study demonstrated a probability of SROT of 23.6% in a diverse and largely chronic group of adult patients with ITP.

KEYWORDS
anti-platelet antibodies, immune thrombocytopenia, indium-111 platelet scintigraphy, thrombopoietin receptor agonist

INTRODUCTION

Patients with immune thrombocytopenia (ITP) have isolated low platelet counts (PCs) (<100×10^9/L) due to accelerated platelet destruction and impaired platelet production.[1,2] The pathophysiological mechanisms underlying ITP are highly diverse.[2,3] Anti-platelet antibodies (APAs) target glycoprotein complexes on the platelet membrane and facilitate Fc- or complement-mediated destruction in the spleen and/or liver.[2] Furthermore, changes in the number and function of T-cells, myeloid-derived suppressor cells (MDSCs) and dendritic cells are observed.[4–6] Currently, ITP is diagnosed by excluding other likely causes of thrombocytopenia.[3] In addition, detection of APAs by the Monoclonal Antibody Immobilization of Platelet Antigen (MAIPA) assay can support the diagnosis of ITP in some patients (50%–80%).[2,7–9] While minimizing bleeding risk and increasing PCs are still the main focus of most ITP treatment strategies, improvement of the patients' quality of life (QoL) gains greater emphasis.[10–13]

Thrombopoietin receptor agonists (TPO-RAs, including romiplostim) are recommended as a subsequent treatment for patients who failed first-line treatment with corticosteroids.[14] TPO-RAs mimic the effects of endogenous TPO by binding to the c-MPL receptor on platelet precursor cells, resulting in initial platelet responses in 75%–95% and durable responses (>6 months) in 65% of patients with ITP.[3,14,15] TPO-RAs are considered a continuous therapy, leading to high healthcare costs and a burden for patients lacking treatment-free intervals.[16,17] Surprisingly, however, recent studies showed that a durable clinical remission can be reached in 15%–50% of patients with ITP upon TPO-RA discontinuation.[18–20] These findings suggest a possible immune-modulating effect via hitherto unknown mechanisms.[15,16,18–20] This evidence is further strengthened by a previous active ITP mouse model showing a decrease in APAs after TPO-RA treatment.[21] The rapid increase in platelet mass induced by TPO-RAs is one of the proposed mechanisms, as platelet-derived transforming growth factor beta 1 (TGF-β1) has been shown to polarize MDSCs towards a more immune suppressive phenotype in this setting.[22,23] The biggest clinical challenge is that there are no clear parameters or biomarkers available that can predict for whom TPO-RA tapering might be beneficial.[18] A recent study suggested that the overexpression of CD69 on CD8 T-cells might be a marker of active immune response and thus a non-sustained response (NSR), but these results require validation.[18,24]

The STIP (Stop TPO-Receptor Agonist in ITP Patients) study aimed to investigate the rate of sustained remission off-treatment (SROT) and to evaluate the clinical effects of romiplostim tapering in patients with persistent or chronic ITP. Hence, we investigated alterations in platelet scintigraphy parameters and APA levels before, during and after romiplostim treatment. In this way, we would like to shed further light on the immunomodulatory effects of romiplostim and to provide starting points for further research on biomarkers predictive of or associated with SROT after TPO-RAs.

METHODS

Study design

The STIP study is a multicenter prospective single-arm intervention study. At inclusion, romiplostim treatment was initiated (T-1) or continued (if <3 months of use). During the first 1–3 months after the start of romiplostim, the response was assessed. Response to romiplostim was defined as having PCs >30×10^9/L and doubling of PCs compared to baseline in the absence of significant bleedings. In case of a response, romiplostim treatment was continued. After 1 year of treatment, romiplostim was tapered within 6 weeks and patients were followed up until 1 year after the start of the tapering (Figure 1). The study was approved by the Medical Ethics Committee Leiden-Den Haag-Delft (approval number: 58678.098.16) and conducted in accordance with the Declaration of Helsinki. Written informed consent was collected prior to inclusion in the study.

Study population

Included patients were adults (≥18 years) with a confirmed diagnosis of primary ITP for ≥3 months who failed at least first-line treatment with corticosteroids or intravenous immunoglobulin (IVIG). Moreover, all patients had a clinical treatment indication at inclusion or were on TPO-RA treatment <3 months after having a treatment indication (Supporting Information, Methods). Potential participants were excluded if they had a previous splenectomy (inability to undergo sequestration studies), secondary ITP, a pregnancy or other comorbid haematological or liver diseases.

Dosing and tapering of romiplostim

Romiplostim was administered subcutaneously and started at a dose of 1–3 mcg/kg once a week.

Dosage modifications were made by the treating physician with the aim of increasing the dose by 1 mc/kg until PC > 100×10^9/L or maximal dosage (10 mcg/kg). After 1 year of treatment, romiplostim was tapered per study protocol. Every 2 weeks, the dose of romiplostim was cut in half in two to three steps (4–6 weeks in total). PCs were evaluated weekly within the first 6 weeks of tapering. Afterwards, the PCs were evaluated at least at 3 months (T3) and 12 months after starting tapering (T4) and more frequently if deemed necessary. The tapering scheme was

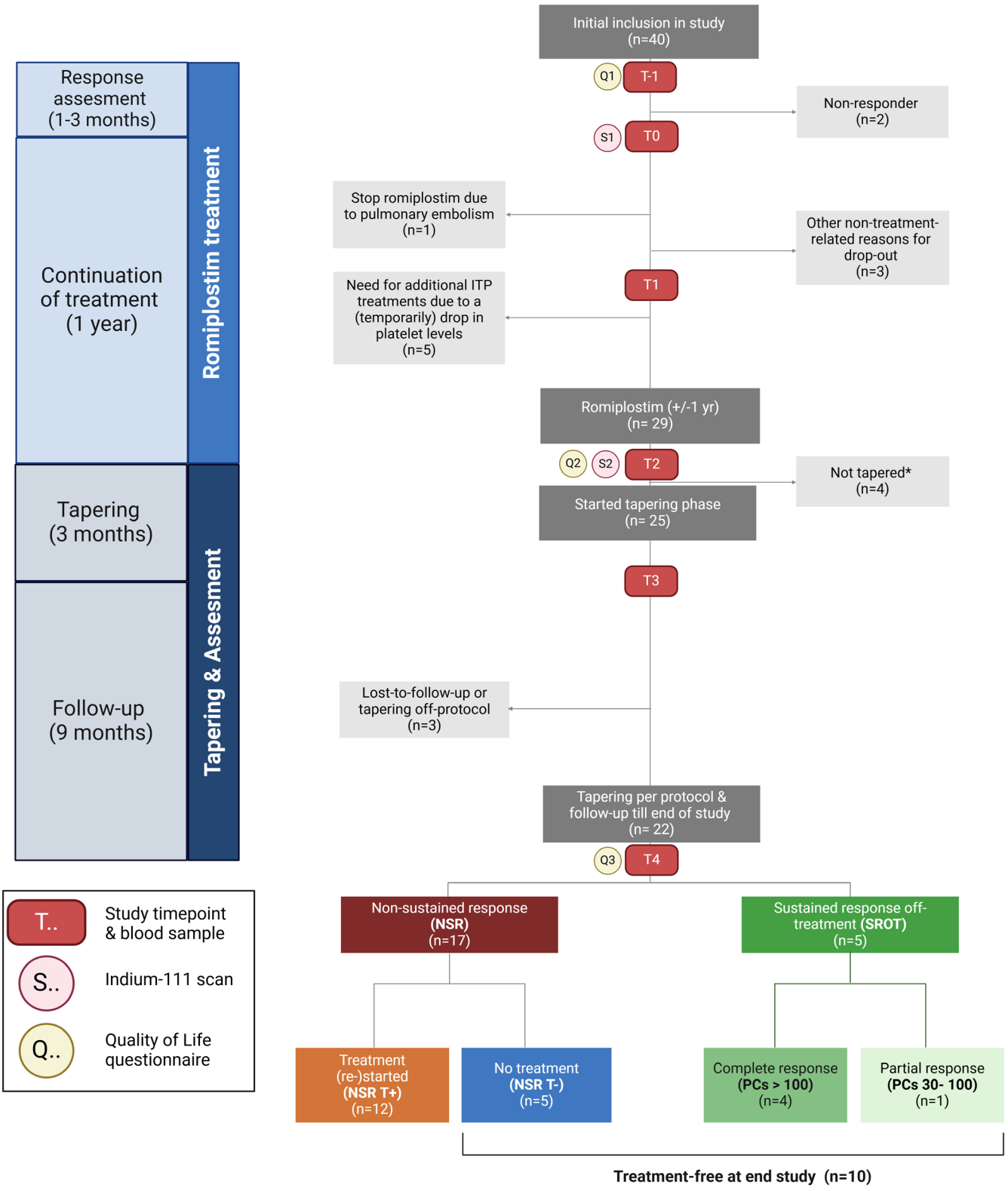

FIGURE 1 Flowchart STIP study. *Reasons not to taper included: The patient did not wish to taper due to personal reasons ($n = 2$), the physician did not want to taper ($n = 1$) and romiplostim was stopped due to an adverse event ($n = 1$). ITP, immune thrombocytopenia; NSR, non-sustained response; PC, platelet counts; SROT, sustained remission off-treatment; STIP, Stop TPO-Receptor Agonist in ITP Patients. [Colour figure can be viewed at wileyonlinelibrary.com]

discontinued if PCs were $< 30 \times 10^9$/L or bleeding symptoms occurred. If one or more relapse criteria were met during the study, it was left to the treating physician's discretion in shared decision-making with the patient to decide whether and which treatment regimen was (re) initiated.

Primary outcome

The primary outcome was the proportion of patients having a SROT at 12 months (T4). An SROT was defined as having 1: PC > 30×10^9/L, 2: no bleeding symptoms (World Health Organization [WHO] ≥1) and 3: not having received (rescue) treatment for ITP at all evaluation visits. If a patient failed to meet these criteria, he or she was considered to have an NSR.

Secondary outcomes

Secondary outcomes include the proportion of patients with an SROT at 3 months (T3) and a complete SROT (SCROT, PC > 100×10^9/L at all visits) at 12 months. Moreover, we assessed the outcomes of patients with NSR who did restart treatment (NSR-T+) and those who did not (re)initiate any ITP treatment (NSR-T–) until the end of the study separately. QoL was measured at the start of the study (T-1), the start of tapering (T2) and the end of the study (T4) with the Dutch ITP (D-ITP) and the Short Form-36 (SF-36) questionnaire[23,24] (Supporting Information, Methods).

Blood samples were drawn at six fixed timepoints during the study (Figure 1). For every timepoint, MAIPA assays and enzyme-linked immunosorbent assays for endogenous TPO levels were performed at Sanquin Diagnostic Services, as described previously.[8] The MAIPA test was used to detect platelet antibodies (anti-GPIIb/IIIa, anti-GPIb/IX and anti-GPV), both directly bound to patients' platelets and indirectly as circulating antibodies in serum. The MAIPA test was considered to be positive if the optical density (OD) value was ≥0.130.[8] Endogenous TPO levels were reported in absolute values (normal: 4–32 IE/mL). Indium-111-labelled platelet scintigraphy was employed to assess changes in the site of platelet sequestration and the rate of platelet clearance during romiplostim. The indium-111 scan was performed twice during the study: before or within 3 months after the start of romiplostim (T-1 or T0) and after 1 year of treatment (T2). The platelet sequestration site and circulatory platelet-associated radioactivity (cPAR) were evaluated at $t = 0.5$, $t = 3$, $t = 24$ and $t = 48$ h after reinfusion, in accordance with the standardized protocol and described previously.[9] Platelet sequestration was expressed as the splenic:liver (S:L) ratio at 48 h after reinfusion and was further stratified into sequestration patterns using previously published definitions.[9] Platelet clearance rate was assessed by cPAR levels at 48 h. A substantial decrease in clearance rate was defined as a decrease of at least 10% cPAR between scans with at least 62% of cPAR left at 48 h, based on our observations in healthy subjects.[25]

Data analysis and statistics

Kaplan–Meier survival analysis was performed to evaluate SCROT and treatment-free rates. Summary statistics and (non-)parametric tests were used to describe the different outcome groups. A p-value <0.05 was considered to be statistically significant. RStudio (version: 2023.09.1) was used for data analysis and visualization.

RESULTS

Baseline characteristics

Forty patients with ITP were included between July 2017 and January 2021 (Figure 1). Baseline characteristics are listed in Table 1. Seventy-five percent (30/40) of the included patients had chronic ITP and 40% (16/40) had received two or more treatment lines prior to inclusion. Half of the patients (18/36) who had not already started romiplostim experienced bleeding symptoms at inclusion with a median PC of 32.5×10^9/L (interquartile range: $17.3–45.3 \times 10^9$/L) (Table 1). Twenty-nine of the 40 patients (72.5%) had a long-term response to romiplostim after 1 year (T2, Figure 1). Of the 29 patients completing 1 year of romiplostim treatment, the median response time (PC >100×10^9/L) was 15 days (range: 0–358 days). Furthermore, a median PC of 132×10^9/L (range: $52–568 \times 10^9$/L) was observed ±3 months after the start of romiplostim. Four patients did not taper due to patients' or physicians' preferences or an adverse event (microangiopathy) requiring abrupt discontinuation. Eventually, 25 patients started tapering (Figure 1).

Primary outcome

Censored Kaplan–Meier analysis of the 25 patients who started tapering revealed that the probability of SROT was 33.1% (95% confidence interval [CI]: 18.2%–60.1%) at 3 months and 23.6% (95% CI: 11.0%–50.5%) at 1 year after tapering (Figure 2). The median time to relapse was 58 days (lower 95% CI: 36 days, upper: not observed). Moreover, 4/5 (80%) SROT patients with complete follow-up had an SCROT (Figure 1). Furthermore, the probability of being treatment free was 46.3% (95% CI: 29.5%–72.6%) at 1 year after tapering and the median time to restart therapy was 113 days (lower 95% CI: 58 days, upper: not observed) (Figure 2).

Safety

Only mild bleeding symptoms (WHO grade 1) were reported after tapering in 41.2% (7/17) of patients with an NSR (Table S1). One patient with mild bleeding symptoms was hospitalised during tapering for monitoring of severe thrombocytopenia (<1×10^9/L). This patient received dexamethasone and recovered quickly. No other adverse events related to discontinuation of romiplostim were reported. Adverse events during romiplostim treatment are listed in Table S2. Twelve patients restarted romiplostim, of which 83.3% (10/12) responded again (Table S1).

TABLE 1 Baseline characteristics ($n = 40$).

				***N* (%) if not otherwise specified**
Female				26 (65%)
Age, years, median (range)				49 (18–80)
ITP duration at inclusion				
<3 months				1 (2.5%)
3–12 months				9 (22.5%)
>12 months				30 (75%)
Previous treatment(s)				
Corticosteroids				39 (97.5%)
IVIG				16 (40%)
Rituximab				13 (32.5%)
TPO-RA <3 months				7 (17.5%)
Previous treatment lines				
One				24 (60%)
Two or more				16 (40%)
Co-medication at inclusion				
Anticoagulation				1 (2.5%)
Prednisone tapering scheme				7 (17.5%)
Already started TPO-RA <3 months				4 (10%)
Other immune suppressants[a]				2 (5%)
Medical history				
Previous solid malignancy				3 (7.5%)
Kidney disease				1 (2.5%)
Diabetes mellitus				4 (10%)
H. pylori eradication				3 (7.5%)
Other autoimmune disease[a]				2 (5%)
ITP characteristics at inclusion				
Before romiplostim start ($n = 36$)				
Median platelet count (IQR) ($\times 10^9$/L)				32.5 (17.3–45.3)
Bleeding symptoms				18 (50%)
WHO grade I				16 (88.9%)
WHO grade II				2 (11.1%)
With romiplostim <3 months ($n = 4$)				
Median platelet count (IQR) ($\times 10^9$/L)				51 (38.3–116.8)
Bleeding symptoms				0 (0%)
	Total	**Only direct**	**Only indirect**	**Both**
MAIPA positive[b] (*n*) at baseline for				
GPIIa/IIIb	10 (25%)	4	1	5
GPIb/9	9 (22.5%)	3	1	5
GPV	8 (20%)	4	1	3
Patients with at least one positive MAIPA test	14 (35%)			

Abbreviations: GP, glycoprotein; *H. pylori*, *Helicobacter pylori*; IQR, interquartile range; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; MAIPA, Monoclonal Antibody Immobilization of Platelet Antigen; OD, optical density; TPO-RA, thrombopoietin receptor agonist; WHO, World Health Organization.

[a]Hydroxychloroquine and methotrexate for Sjögren's disease and rheumatoid arthritis respectively.

[b]Positive MAIPA is defined as an OD value of 0.130 or higher. Direct MAIPA detects platelet-bound antibodies. Indirect MAIPA detects circulating antibodies.[8]

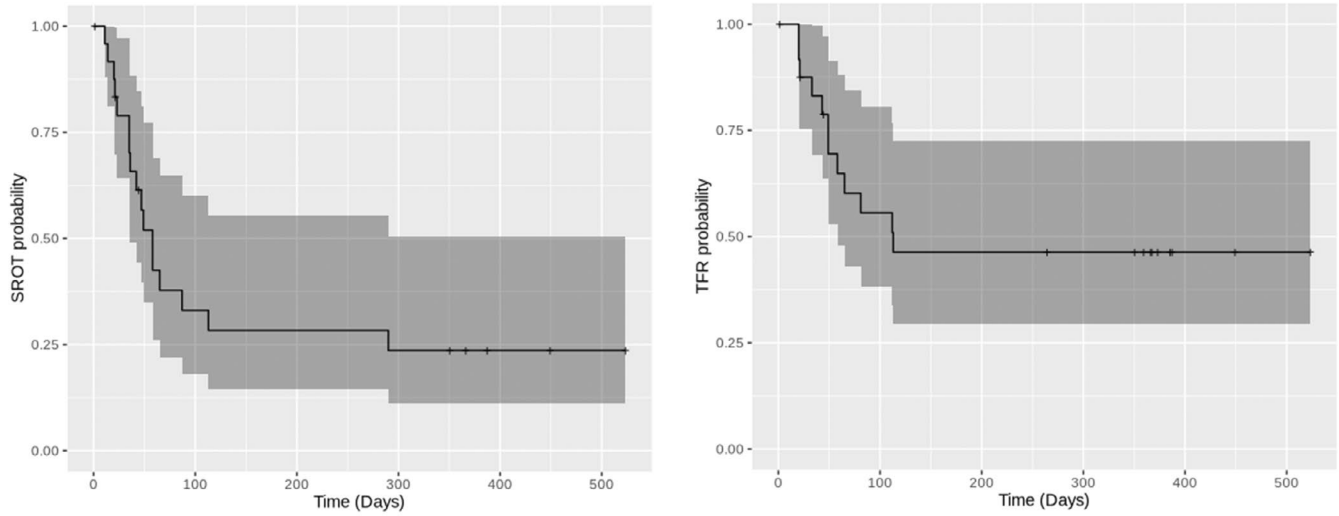

FIGURE 2 Kaplan–Meier curves of primary outcomes (SROT and TFR) (left = time to relapse, right = time to restart). SROT, sustained remission off-treatment. TFR, treatment free response.

Clinical predictors

Patients with an SROT reached higher platelet levels (median: 332.5 vs. 84.5 × 10^9/L) during romiplostim and had lower stable doses at the start tapering (median: 1.0 vs. 4.5 μg/kg) compared to those with an NSR (Table 2). The amount of previous treatment lines was evenly distributed between outcome groups. The median age for those with an SROT and an NSR was 25 and 56 years respectively. APAs were detected at baseline in 8/25 (32%) patients who tapered romiplostim, of which 5 (SROT: 2/3, NSR: 3/5) showed a substantial decrease (OD value ≥0.10) in antibody levels (Table 3; Figure S3). We found that the endogenous TPO levels at the start of the tapering were similar for patients with an SROT and NSR (median: 13 vs. 10.5 IE/mL, Table 3; Figure S4).

Thirty-two patients had their first scan <3 months after the start of romiplostim. In this cohort, 31.3% (10/32) had a splenic, 40.6% (13/32) a mixed and 28.1% (9/32) a hepatic pattern (Table 4). After 1 year of romiplostim, 14 patients switched from a sequestration pattern, with 21.4% (3/14) changing from splenic to non-splenic (hepatic/mixed) (Table 4). Within the total group who tapered (available: $n = 20$), the scans showed no significant change in the median S:L ratio (1.22 vs. 1.33, $p = 0.81$). However, for patients with a SROT, the median S:L ratio increased by 0.6 (range: 0.1–1.9), while this was not observed in those with an NSR (median difference: 0.0 [range: −1.8–1.4], $p = 0.02$, Figure S5). The median cPAR at 48 h was 41.7% for the first and 42.2% for the second scan in those who tapered ($p = 0.44$). A substantial decrease in the clearance rate between scans was noted in 50% (2/4, missing $n = 1$) of patients with an SROT compared to 0% (0/14, missing $n = 3$) in the NSR group (Table 3; Figure 3). Notably, 1 patient with an SROT and 1 patient with an NSR already had clearance rates within normal ranges (>62% cPAR at 48 h) at the first scan (Figure 3). The platelet clearance rate did not differ significantly between patients with or without APAs during both scans ($p = 0.91$ and $p = 0.84$).

QoL

For the D-ITP questionnaire, we observed a relevant increase in 3/11 domains for those who were treatment free at the end of the study and in 4/11 domains for those who were not (Table S5). Both groups improved within the Fatigue and Psychological Health domains. The SF36 questionnaire, however, showed minor changes (Table S6).

DISCUSSION

In this study, we showed a probability of SROT of 23.6% at 1 year after romiplostim tapering in adults with persistent or chronic ITP. Our SROT rate is lower compared to previous studies (Table S3[18,24–29]). The cohort study by Guillet et al.,[18] for example, showed a much higher SROT rate of 52.1%, but only included patients with a complete response (PCs >100 × 10^9/L) on TPO-RAs. This selection criterion alone may have yielded higher SROT rates, as we, amongst others, have shown that patients with SROT tend to have higher PCs during treatment.[26] Furthermore, the iROM study included patients before the start of romiplostim, but all patients with an SROT (6/13, 46%) had newly diagnosed ITP (<4 weeks).[26] In our cohort, only one SROT patient had ITP for <12 months. The median ITP duration for those with SROT was 132.4 months, longer than NSR patients, limiting the likelihood of spontaneous remission (Table 2).

Strikingly, the probability of being treatment free for the entire 12 months after tapering was 46.3%. Even though some patients had one or more PCs below 30 × 10^9/L, romiplostim was not restarted. Various physician- and patient-specific

TABLE 2 Clinical characteristics of patients after romiplostim tapering. [Colour table can be viewed at wileyonlinelibrary.com]

	SROT	NSR-T–	Treatment free[a]	NSR-T+	Off-protocol before end study	Total of tapered patients
	N = 5	*N* = 5	*N* = 10	*N* = 12	*N* = 3	*N* = 25
Baseline						
Age (years, median, range)	25 (19–65)	57 (28–75)	56 (19–75)	56 (21–80)	48 (21–63)	54 (19–80)
Female (*n*, %)	4 (80%)	2 (40%)	6 (60%)	8 (66.7%)	2 (66.7%)	16 (64%)
Median ITP duration at inclusion (months)	132.4 (2.8–455.1)	16.7 (3.8–97.0)	16.8 (2.8–455.1)	53.6 (9.2–166.6)	77.7 (8.2–193.6)	48.3 (2.8–455.1)
Patients with ITP <12 months (*n*, %)	1 (20%)	1 (20%)	2 (20%)	1 (8.3%)	2 (66.7%)	5 (20%)
Two or more previous treatment lines (*n*, %)	3 (60%)	3 (60%)	8 (60%)	6 (50%)	3 (100%)	12 (48%)
Rituximab in history (*n*, %)	3 (60%)	3 (60%)	6 (60%)	4 (33%)	0 (0%)	10 (40%)
Treatment						
Time until platelets $>100\times10^9$/L (days, median, range)	9 (0–79)[b]	16 (7–263)	13 (0–263)	16 (7–358)	32 (7–217)	15 (0–358)
Median platelet count at ±3 months after start (range)[c]	151 (125–374)	154 (61–568)	152.5 (61–568)	75 (52–237)	109 (77–222)	132 (52–568)
Median platelet count during stable romiplostim treatment ($\times10^9$/L, range of medians)	332.5 (143–342)	123 (78–217)	217 (78–342)	81.5 (37–241)	66 (66–115)	99 (37–342)
Platelet count $>100\times10^9$/L at start of tapering (*n*, %)	4 (80%)	4 (80%)	8 (80%)	6 (50%)	0 (0%)	14 (56%)
Romiplostim dosage at start of tapering (μg/kg, median, range)	1.0 (0.5–2.0)	3.0 (1.2–5.0)	1.4 (0.5–5.0)	5.0 (0.5–9.0)	1.0 (0.5–5.0)	3.0 (0.5–9.0)
Duration of romiplostim treatment (months, median, range)	12.4 (7.7–14.7)	12.7 (12.1–16.2)	12.5 (7.7–16.2)	13.6 (10.9–16.3)	11.9 (11.2–12.9)	12.8 (7.7–16.3)

Abbreviations: ITP, immune thrombocytopenia; NSR, non-sustained response; SROT, sustained remission off-treatment.

Note: Color shades indicate the total number (either total of treatment-free patients (NSR-T- and SROT patients) or the overall total).

[a]Treatment free are the patients who had an SROT and the patients who relapsed but did not restart any treatment combined.

[b]One participant already started with eltrombopag and already had a platelet count $>100\times10^9$/L when switching to romiplostim at inclusion.

[c]Ranges from 67 to 119 days from start (median: 92 days).

factors might have influenced this decision. We do regard being treatment free an important clinical end-point, as these patients did require therapy before inclusion and are now free from the burden of continuous therapy and (long-term) side effects.[30–32] Furthermore, a post hoc sensitivity analysis of patients with PCs <30 vs. $>30\times10^9$/L at inclusion revealed comparable SROT and treatment-free rates (Figures S1 and S2).

Only mild, well-manageable bleedings were observed, verifying that tapering romiplostim is relatively safe if PCs are frequently monitored and a gradual tapering scheme is followed. In line with previous work, we confirmed that patients who were younger, responded with higher PCs to romiplostim and had lower stable doses were more likely to achieve SROT.[18,26] We used a tapering scheme of 6 weeks, while a dose-dependent scheme with a longer duration has been suggested by others.[19,33] Our scheme might have been too short for patients on higher romiplostim doses because of too large steps in dose reduction, potentially limiting their SROT probability. Furthermore, our findings suggest that if patients respond to romiplostim with improved platelet production, this may add to platelet-mass-driven mechanisms of immunomodulation. Some platelet-driven mechanisms have already been investigated, including platelet-derived TGF-β1, induction of T-cell energy or platelets binding to monocytes.[22,23,34–36]

A unique feature of this study is the longitudinal evaluation of both APA and endogenous TPO levels (Figures S3 and S4). APAs were only detected in 14/40 (35%) of patients at inclusion, which is lower than previously reported (50%–80%).[7,8,37] Poor diagnostic validity is unlikely as the MAIPA assay is thoroughly validated in our institute and all patients have been diagnosed in accordance with the D-ITP guidelines.[8,38] The low APA positivity rate is most plausibly

TABLE 3 Laboratory and scan characteristics of patients after romiplostim tapering. [Colour table can be viewed at wileyonlinelibrary.com]

	SROT ($n=5$)	NSR-T– ($n=5$)	Treatment free[a] ($n=10$)	NSR-T+ ($n=12$)	Off-protocol before end of study ($n=3$)	Total of tapered patients ($n=25$)
APAs						
Detectable APAs at baseline (n, %)	3 (60%)	1 (20%)	4 (40%)	4 (33.3%)	0 (0%)	8 (32%)
Substantial decrease in APAs between baseline and start tapering (n, %)[b]	2 (40%)	1 (20%)	3 (30%)	2 (16.7%)	0 (0%)	5 (20%)
Detectable APAs at end of the study in those with APAs at baseline (n, %)	3 (60%)	0 (0%)	3 (30%)	2 (16.7%)	0 (0%)	5 (20%)
	$N=5$	**$N=5$**	**$N=10$**	**$N=11$ 1 missing**	**$N=1$ 2 missing**	**$N=22$ 3 missing**
Platelet turnover markers						
Median TPO level at start of tapering (IE/mL, range)	13 (4–25)	9 (5–12)	10 (4–25)	11 (4–41)	5	10.5 (4–41)
	$N=5$	**$N=4$ 1 missing**	**$N=9$ 1 missing**	**$N=9$ 3 missing**	**$N=2$ 1 missing**	**$N=20$ 5 missing**
Scan sequestration site						
Difference in S:L ratio between scans (T2-T0, median, range)	0.6 (0.1–1.9)	0.2 (−0.6–1.4)	0.3 (−0.6–1.9)	−0.1 (−1.8–0.3)	0.2 (−0.1–0.4)	0.0 (−1.8–1.9)
Splenic sequestration pattern at start of tapering (n, %)	3 (60%)	1 (25%)	4 (44.4%)	2 (22.2%)	1 (50%)	7 (35%)
Swift from non-splenic to splenic pattern (n, %)	2 (40%)	1 (25%)	3 (33.3%)	0 (0%)	0 (0%)	3 (15%)
	$N=4$ 1 missing	**$N=4$ 1 missing**	**$N=8$ 2 missing**	**$N=10$ 2 missing**	**$N=2$ 1 missing**	**$N=20$ 5 missing**
Scan clearance rate						
Clearance rate within normal range at start of tapering (T2) (≥62% cPAR)	3 (75%)	1 (25%)	4 (50%)	0	1 (50%)	5 (25%)
Clearance rate within normal range at first scan (<4 months after start of romiplostim) (≥62% cPAR)	1 (25%)	1 (25%)	2 (25%)	0	0	2 (10%)
Improvement in clearance rate of ≥10% cPAR	2 (50%)	0 (0%)	2 (25%)	4 (40%)	1 (50%)	7 (35%)

Abbreviations: APAs, anti-platelet antibodies; cPAR, circulatory platelet-associated radioactivity; MAIPA, Monoclonal Antibody Immobilization of Platelet Antigen; NSR, non-sustained response; OD, optical density; S:L, splenic:liver; SROT, sustained remission off-treatment; TPO, thrombopoietin.

Note: Color shades indicate the total number (either total of treatment-free patients (NSR-T- and SROT patients) or the overall total).

[a]Treatment free are the patients who had an SROT and the patients who relapsed but did not restart any treatment combined.

[b]Decrease of at least 0.10 OD in either the direct or indirect MAIPA or both types was regarded as a substantial decrease.

explained by the fact that many participants had received multiple lines of treatment prior to inclusion leading to seroconversion,[39–41] which may have skewed the cohort to those with more T-cell driven disease. Like previous studies,[21] we observed a substantial decrease, though not a complete disappearance, in APAs during romiplostim treatment in some patients (Figure S3). The clinical significance of this finding, however, remains unclear. Only one other study explored the relationship between TPO levels and SROT, with findings also indicating an absence of correlation.[28] Furthermore, in line with previous studies,[42] we observed higher TPO levels at inclusion for the patients who did not respond to romiplostim (Table S4).

A decreased platelet clearance rate combined with a normalized cPAR at 48 h (>62%) might be an indicator of biological remission, although more data are necessary to confirm this. We found no significant skewing of platelet sequestration towards either a splenic or hepatic pattern after romiplostim. These findings are supported by two previous studies that did not identify a significant difference in the site of sequestration between untreated patients and those with TPO-RAs.[43,44]

However, the majority of patients (14/23, 61%) in our study changed from sequestration patterns over time with individual S:L ratio differences ranging from −1.80 to 1.90 (median: 0.07). This is in contrast to our study in healthy adults in

which we showed that sequestration patterns are relatively stable over time.[25] Only one other study gathered longitudinal sequestration data before and after 5 months of TPO-RAs.[45] They found a change in sequestration pattern in 3 of 8 (37.5%) patients, all from splenic to mixed.[45] A longitudinal change in sequestration pattern might indicate a therapeutic or disease-specific effect. More importantly, our observation that sequestration patterns might change over time raises questions about the timing of platelet scintigraphy as a predictor for splenectomy and should be further investigated. Due to the limited number of patients with APAs, we could not validate previously identified associations between sequestration site, TPO levels and APAs.[9,46]

Limitations of this study are the descriptive nature of this cohort study, the limited study size for secondary outcomes and the limited time of 1 year follow-up after tapering. Moreover, two patients had concurrent autoimmune diseases (Table 1), for whom we cannot eliminate the possibility of secondary ITP. Furthermore, we studied romiplostim, which is the only TPO-RA that binds to the extra-cellular domain of the MPL receptor and has an Fc part. Hence, as the potential tolerogenic activity of the Fc fragment has been hypothesized,[47] our results might not directly apply to other types of TPO-RA.

Taken together, the STIP study showed that in patients with many years of chronic ITP and in those who had received multiple treatment lines, an SROT can be reached in 23.6%. While these patients had a clinical remission, we could only validate this biologically with 75% having normal cPAR levels (>62%) and not with our APA assays. Platelet-mass-induced immune modulatory effects are the most likely course of action and should be further investigated.

TABLE 4 Sequestration patterns. [Colour table can be viewed at wileyonlinelibrary.com]

T0—Start of romiplostim		T2 ±1 year of romiplostim			
	Total T0	**Splenic**	**Mixed**	**Hepatic**	**Missing**
Splenic	**10**	4	2	1	3
Mixed	**13**	4	4	2	3
Hepatic	**9**	1	4	1	3
Missing	**4**	0	0	1	3
Total T2	**36**[a]	**9**	**10**	**5**	**12**

Note: Dark blue color shades and bold font indicate the total number, light blue color shades indicate patients who had similar platelet sequestration pattern at T0 and T2.

[a]Four patients were excluded because of first scan >4 months after start of romiplostim.

AUTHOR CONTRIBUTIONS

The study was designed by MRS and SNA. SNA and VSN were coordinating researchers during the study period,

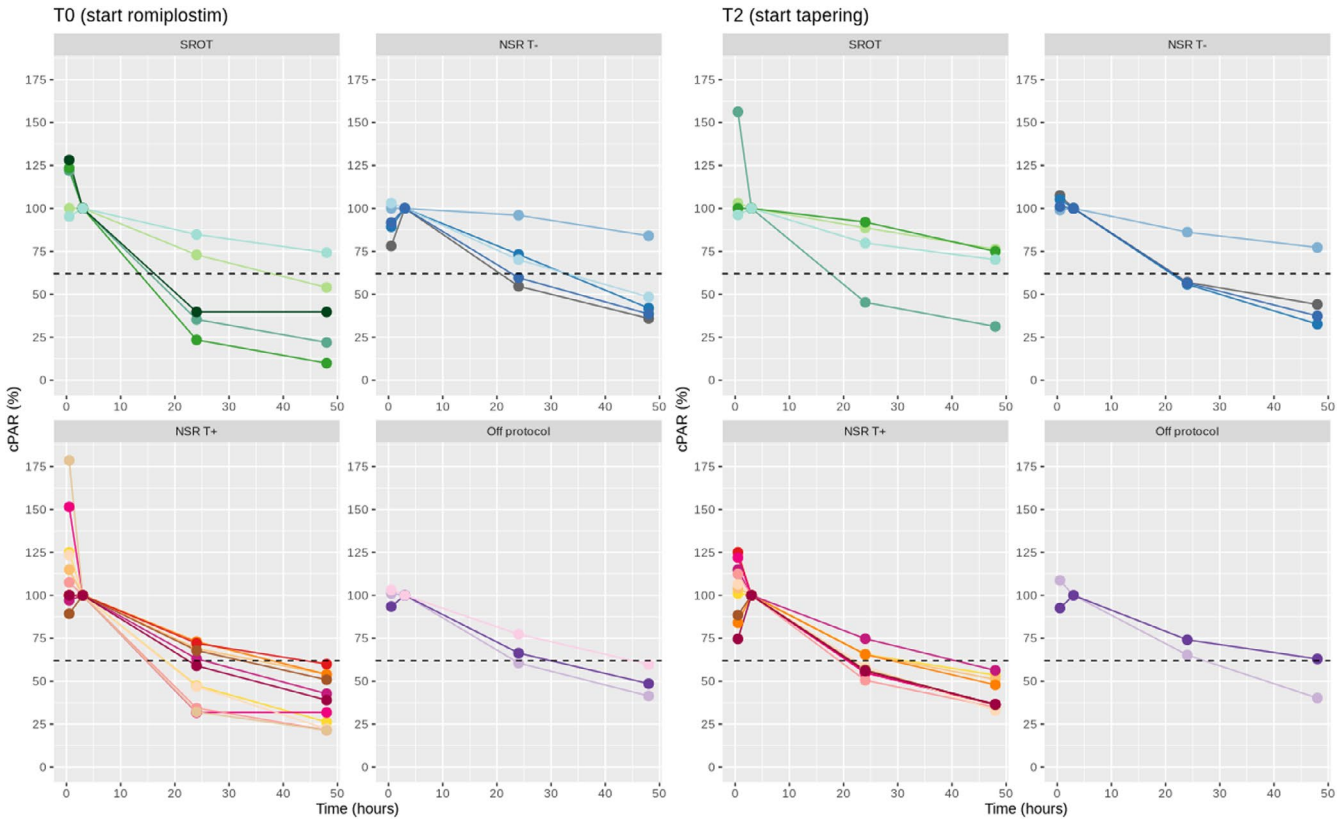

FIGURE 3 Circulating platelet-associated radioactivity during the scan period for both scans (T0 and T2). cPAR, circulatory platelet-associated radioactivity; NSR, non-sustained response; SROT, sustained remission off-treatment. [Colour figure can be viewed at wileyonlinelibrary.com]

supervised by MRS and TN at the Haga Teaching Hospital. REGS, OV, PEW and JJZ supervised research teams at the other included institutions. MdH, LP and SH-vE supervised the MAIPA and TPO testing and the staff of the platelet and leukocyte serology laboratory. The scans were performed by technicians of the Nuclear Medicine Department of the Haga Teaching Hospital. MSK supervised the scan procedure and analysed scan images. VSN analysed the data and wrote the original draft. MRS, TN, RK, MdH and VSN took part in work discussions and data analysis interpretation meetings. All authors reviewed and edited the original draft.

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CONFLICT OF INTEREST STATEMENT

All authors have confirmed that there are no relevant conflicts of interest to report.

DATA AVAILABILITY STATEMENT

For original data, please contact one of the corresponding authors.

CLINICAL TRIAL REGISTRATION

This trial was registered at https://onderzoekmetmensen.nl/en/trial/22827 (the Dutch Trial Register) as #NL6605.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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