Management of Adult Patients with Newly Diagnosed or Relapsed Primary Immune Thrombocytopenia in Eastern Austria

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Abstract

Background Treatment sequence in primary immune thrombocytopenia (ITP) is based on national and international recommendations, treatment availability, and physician expertise.

Aim This article aimed to provide real-world data on treatment sequence and responses to first- and second-line treatments in newly diagnosed and relapsed adult ITP patients.

Methods We analyzed a cohort of 46 adult ITP patients from the Vienna ITP Biobank, who started first-line therapy within 1 week before their first study visit between February 2016 and March 2023. We investigated clinical patient characteristics and patient management in our specialized center and examined the impact of the international ASH guidelines on ITP treatment.

Results Forty-six primary ITP patients, 27 (58.7%) with newly diagnosed ITP and 19 (41.3%) with relapsed ITP, were investigated. Most patients were female (65.2%) with a median platelet count of 9×10^9/L, and 31 patients (67.4%) had bleeding symptoms. All patients received first-line treatment with oral prednisolone; 15 patients received oral prednisolone combined with intravenous immunoglobulins (IVIGs), which were more commonly administered in newly diagnosed than in relapsed ITP patients. First-line therapy resulted an overall response in 82.6% of patients after a median (interquartile range [IQR]) time of 10 (5–25) days. There was no difference in treatment responses between newly diagnosed and relapsed ITP patients, but newly diagnosed patients had a shorter time to response (median [IQR]: 8 [5–14] and 14 [8–27], $p = 0.02$). Twenty-three (50%) of the patients (11/27 newly diagnosed [40.7%], 12/19 relapsed [63.2%]) required second-line ITP therapy. Thrombopoietin-receptor agonists (TPO-RAs) were the most commonly used second-line therapy with a response rate of 73.7%, and a median (IQR) time to treatment response of 15 (12–20) days. Overall response rates to TPO-RA treatment did not differ between newly diagnosed and

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relapsed ITP. Following the publication of novel guidelines in 2019, the median (IQR) duration of corticosteroid treatment shortened (100–52 days, $p = 0.01$), as did the time to second-line treatment (160–47 days, $p = 0.01$), and the median number of first-line therapies decreased from 2 (1–3) to 1 (1–2).

Conclusion Initial treatment with corticosteroids was effective in the majority of newly diagnosed and relapsed ITP. Response rates to initial corticosteroid treatment in ITP patients are consistent with previous data, but only 50% achieve sustained remission. TPO-RAs, which are well tolerated and effective, are the most commonly used second-line therapy in our study population. International guidelines have led to faster treatment transitions and reduced splenectomy rates. Integration of real-life experience, expert consensus, and guidelines optimizes ITP patient management.

Introduction

Primary immune thrombocytopenia (ITP) is a rare acquired autoimmune disease, characterized by an isolated low platelet count ($<100 \times 10^9$ /L) in the absence of other causes of thrombocytopenia.[1,2] Clinical symptoms of primary ITP include an increased bleeding risk ranging from mild bruising and mucosal bleeding to massive hemorrhage[3,4] as well as physical and mental fatigue.[5] Primary ITP is a diagnosis of exclusion, as there is no clinical or laboratory parameter to confirm diagnosis. Furthermore, no clinically applicable biomarkers to risk-stratify patients or predict the course of disease (self-limiting, relapsing, and chronic) and treatment responses are available. Therefore, the management and treatment of patients with ITP bear special challenges and require profound experience.

In Austria, besides the current international American Society of Hematology (ASH) guidelines,[6,7] ITP treatment follows local recommendations of the German, Austrian, and Swiss working groups which are frequently updated.[8] In both guidelines, oral corticosteroids, prednisolone, and high-dose dexamethasone are recommended as the long-established first-line therapy to prevent bleeding in primary ITP. The aim of the first-line treatment is to rapidly achieve platelet count responses and thus decrease the bleeding tendency, whereas considerations on tolerability, long-term responses, and long-term toxicity yet have lower priority. First-line treatment with corticosteroids leads to high platelet response rates of around 60%; nevertheless, only 20 to 50% of patients achieve long-term responses.[9] Initially, thrombopoietin-receptor agonists (TPO-RAs) were mostly labeled for use in splenectomized chronic ITP patients or in case of contraindications for splenectomy.[10,11] Nevertheless, their off-label use as splenectomy-sparing agents has been acknowledged early in national and international recommendations.[11] Since then, there has been increasing awareness of the side effects and toxicities of corticosteroid overuse,[12,13] resulting in clear recommendations on the short-term use of corticosteroids and early switch to second-line treatment in international guidelines in 2019.[6,7,10,14] While earlier recommendations and current guidelines recommend TPO-RAs as the preferred second-line treatment,[8,11] ASH guidelines of 2019 still recommend the use of TPO-RA or rituximab or splenectomy as the second-line treatment option with a clear recommendation for shared decision-making with the patient.[14]

Following the recommendations in Austria, TPO-RAs are prescribed early in the course of disease after nonresponse to corticosteroid treatment or side effects or early relapses, which is also now accounted for in the labeling of the TPO-RA, romiplostim and eltrombopag, allowing their use directly after corticosteroid failure.[8,11]

This prospective real-world study investigates the treatment sequences and response to first- and second-line treatments in adult patients with newly diagnosed or relapsed primary ITP in Austria. In the well-characterized cohort, we also provide data on patient characteristics and the clinical bleeding phenotype. Additionally, we analyze changes in the management and treatment of primary ITP patients before and after the publication of the ASH guidelines in December 2019[7,10,14] to assess whether patients have benefitted from the guidelines.

Methods

Study Design and Study Population

This study was performed as a substudy within the Vienna ITP Biobank, a multicenter prospective cohort study established in 2016 at the Department of Hematology and Haemostaseology at the Medical University of Vienna and the Third Medical Department of the Hanusch Hospital, Vienna. The ITP Biobank includes all patients aged $\geq$18 years with a diagnosis of primary ITP according to standard criteria[15] who are newly diagnosed, under observation, or treated at one of the participating centers. Patients with platelet counts $< 100 \times 10^9$ /L without ITP-specific treatment, secondary ITP or hereditary thrombocytopenia, or active malignancy are not included. Within the ITP Bleeding Biobank, patients are prospectively followed up with annual visits in case of chronic and stable ITP. In the case of newly diagnosed or relapsed ITP, follow-up visits are performed after 1 week, 1 month, 3 months, and then annually. All patients give written informed consent before inclusion in the ITP Biobank. The study is conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Vienna (EC1843/2016).

For the present analysis, patients who were included in the Vienna ITP Biobank before February 2023 and started first-line treatment with corticosteroids at study inclusion or within 1 week before study inclusion were selected and followed up prospectively. Overall, 155 primary ITP patients were included in the ITP Biobank before February 2023. Forty-six of them (30%) were started on first-line therapy at study inclusion or within 1 week before study inclusion and thus were included in this data analysis.

Baseline Characteristics

Upon study inclusion and at every follow-up visit, the patients' general medical history as well as the ITP-specific patient history are recorded using a standardized questionnaire. Data include demographic data and data on general health and comorbidities, as well as ITP-specific information, and previous ITP-specific treatments. A trained physician and/or personnel used an ITP-specific standardized bleeding assessment tool to estimate the patients' bleeding severity (SMOG). During routine visits, blood samples are drawn and routine laboratory parameters are generated at the central laboratory, Department of Laboratory Medicine, Medical University Vienna, for routine laboratory investigations. Each patient undergoes a routine blood test to assess blood count, differential blood count, renal and liver function, viral infections with hepatitis A, B, C, and HIV, and parameters of inflammation and immunology.

Evaluation of Treatment Response

Treatments for ITP are systematically recorded in the standardized questionnaires at every follow-up visit and are documented in the hospital information system at every patient visit. For each patient, ITP treatments were cross-checked and platelet counts to evaluate treatment response were completed using the hospital information system.

Criteria for response to treatment were defined following the international Working Group[15]: (1) complete remission (CR) as platelet count $\geq 100 \times 10^9$/L and the absence of bleeding; (2) partial response (PR) as platelet count $\geq 30 \times 10^9$/L and at least twofold increase of the baseline count and absence of bleeding; (3) no response (NR) as platelet count $<30 \times 10^9$/L or less than twofold increase of the baseline platelet count or bleeding. The overall response rate (ORR) includes CR and PR. Time to response was defined as the duration from initiation of treatment to achievement of CR or PR. Duration of response was measured from the achievement of CR or PR to loss of response (platelet count dropped below 30×10^9/L or presence of bleeding) or to the last follow-up visit. ITP relapse was defined as a drop in platelet counts to less than $<30 \times 10^9$/L with the presence of bleeding symptoms or the need to use rescue therapy. The duration of first or second-line treatment was defined as the period starting from the day of the first or second treatment until its end. First-line treatment began on the day when the first oral or infused drug within the initial line of therapy was administered and ended either with the initiation of a new drug or following the end of the previous line of therapy. The line of therapy's discontinuation date was defined as the last day on which a drug in the treatment plan was administered or the final day of the oral medication supply.

Statistical Analysis

Data are presented as numbers and percentages for qualitative variables and median and interquartile ranges (IQR, 25–75th percentile) for quantitative variables. The comparison of variables between the groups of patients with newly diagnosed or relapsed ITP and between treatments before and after 2019 were conducted using chi-square and Fischer's tests for qualitative variables and Wilcoxon's Mann–Whitney test for quantitative variables. We used the Kaplan–Maier curve to determine the duration of remission. Data were considered statistically significant at p-values <0.05. Statistical Package for the Social Sciences Windows version 27.0 (SPSS, Chicago, Illinois, United States) was used to perform all statistical analyses.

Results

Baseline Demographic Data of Primary ITP Patients

Forty-six primary ITP patients, who were started with first-line therapy at or within 1 week before inclusion in the Vienna ITP Biobank, were analyzed. Patients were followed up until February 2023 with a median (min–max) follow-up time of 20 (3–78) months. Of them, 27 patients (58.7%) had newly diagnosed ITP and 19 patients (41.3%) had an acute relapse of remitting–relapsing ITP, with a median disease duration of 69 months. Baseline demographic and clinical characteristics are shown in ►Table 1 for all patients and separately for newly diagnosed and relapsed ITP patients.

The majority of patients were female (65.2%) and the median age was 43 (30–55) years at the time of study inclusion. The median platelet count was 9×10^9/L ($3–20 \times 10^9$/L). The majority of patients (67.4%) reported bleeding symptoms at their initial presentation.

There was no difference in age or sex between newly diagnosed and relapsed ITP patients. The platelet count at treatment initiation was higher in the relapsed group. Eight of the 19 relapsed ITP patients (42.1%) previously received a median of three cycles of first-line therapy. More patients with relapsed ITP had any bleeding manifestation. Nevertheless, the bleeding phenotype was more severe, with bleeding scores >4 points, in newly diagnosed than in relapsed ITP patients (►Table 1).

First-Line Therapy and Treatment Response

All 46 patients received first-line therapy with prednisolone at a median (IQR) starting dose of 1.0 (0.8–1.1) mg/kg body weight (►Table 2). None of the patients received pulsed dexamethasone as first-line treatment. Fifteen patients (32.6%) additionally received intravenous immunoglobulins (corticosteroids + IVIG) with a dose of 1 g/kg body weight/day for 2 consecutive days, which was more frequently given in newly diagnosed than in relapsed ITP patients ($p = 0.01$, ►Table 2).

The median (IQR) duration of treatment with prednisolone was 62 (39–122) days. Outcomes of the first-line

Table 1 Baseline characteristics of all patients ($n = 46$) and according to disease duration

Clinical characteristics	Primary ITP ($n = 46$)	Newly diagnosed ITP ($n = 27$)	Relapsed ITP ($n = 19$)
Female, *n* (%)	30 (65.2)	16 (59.3)	14 (73.7)
Age, years, median (IQR)	43 (30.0–55.0)	50.0 (30.0–56.0)	36.0 (27.0–56.5)
BMI, kg/m^2, median (IQR)	25.5 (23.2–29.8)	25.7 (23.3–30.3)	26.3 (23.4–31.1)
Disease duration, months, mean ± SD	68.6 ± 103.7	0.1 ± 0.3	165.3 ± 150.3
Platelet count, $\times 10^9$/L, median (IQR)	9 (3–20)	5 (2–14)	12 (6–21)
Previous first-line therapy, median (min–max)	2 (0–3)	0.0 (0.0)	3 (2–4)
Any bleeding, *n* (%)	31 (67.4)	17 (63.0)	14 (73.7)
SMOG BS > 4, *n* (%)	20 (43.5)	15 (32.6)	5 (10.8)
Previous thrombosis, *n* (%)	7 (15.2)	4 (14.8)	3 (21.1)

Abbreviations: BMI, body mass index; BS, bleeding score; ITP, immune thrombocytopenia.

Table 2 Outcome of first-line therapy of all patients ($n = 46$) and according to disease duration

	Primary ITP ($n = 46$)	Newly diagnosed ITP ($n = 27$)	Relapsed ITP ($n = 19$)	*p*
Platelet count at treatment initiation, $\times 10^9$/L, median (IQR)	10 (4–20)	7 (2–14)	15 (10–21)	0.04
Platelet count after ITP-specific treatment $\times 10^9$/L) median (IQR)	110 (44–155)	120 (54–159)	107 (34–136)	0.49
Corticosteroid starting dose, mg/kg bodyweight, median (IQR)	1.0 (0.8–1.1)	1.0 (0.7–1.1)	0.9 (0.6–1.1)	0.46
Corticosteroid + IVIG, *n* (%)	15 (32.6)	13 (48.2)	2 (10.5)	0.01
Duration of treatment, days, median (IQR)	62 (39–122)	79 (44–154)	57 (35–96)	0.18
Response rates				
ORR, *n*, (%)	38 (82.6)	22 (81.5)	16 (84.2)	0.83
Time to OR, days, median (IQR)	10 (5–25)	8 (5–14)	14 (8–27)	0.02
CR, *n* (%)	31 (67.4)	19 (70.4)	12 (62.3)	0.61
Time to CR, days, median (IQR)	10 (5–15)	7 (5–14)	14 (10–27)	0.02
PR, *n* (%)	7 (15.2)	3 (11.1)	4 (21.1)	0.36
Time to PR, days, median (IQR)	10 (4–29)	20 (4–20)	9 (3–75)	0.86
NR, *n* (%)	8 (17.4)	5 (18.5)	3 (15.8)	0.81
Duration of response				
Loss of OR, *n* (%)	17 (37.0)	7 (25.9)	10 (52.6)	0.12
Time to loss of OR, days, median (IQR)	90 (20–170)	42 (15–90)	120 (23–390)	0.04

Abbreviations: BS, bleeding score; CR, complete response; IQR, interquartile range; ITP, immune thrombocytopenia; *n*, number; NR, nonresponse; OR, overall response; PR, partial response.

therapy are shown in ►**Table 2** for all patients, and separately for newly diagnosed and relapsed ITP patients.

Of the 46 patients receiving prednisolone, 38 patients (ORR: 82.6%) responded after a median time of 10 (5–15) days, while 8 patients (17.4%) showed NR to *corticosteroid* treatment. Overall, 31 patients (67.4%) achieved a complete response (CR) after a median time of 10 (5–25) days, and 7 patients (15.2%) achieved PR as their best response after a median time of 10 (4–29) days.

Patients with newly diagnosed ITP had significantly lower platelet counts at treatment initiation ($p = 0.04$) than patients with chronic relapsed ITP, and more commonly received additional IVIG. There were no significant differences in the ORR and rates of CR and PR between patients with newly diagnosed and relapsed ITP. Nevertheless, time to OR and CR was significantly shorter in newly diagnosed ITP patients, which might be attributed to the increased rate of additional IVIG administration, as patients with IVIG and prednisolone responded faster than those with prednisolone-only (median (IQR) days to OR response: 8.0 (5.0–14.0) and 14.0 (8.0–27.0); $p = 0.02$).

Twenty-two of 46 patients (47.8%) reported adverse effects with corticosteroid therapy. Insomnia was the most

commonly reported side effect (26.7%), followed by weight gain (20.0%), restlessness and nervousness (15.6%), and skin problems (4.4%).

Relapse and Remission after First-Line Treatment

Of the 38 patients who responded to first-line treatment, 17 relapsed (44.7%) after a median time of 90 days of response, whereas 21 patients (55.3%) achieved long-term remission after first-line treatment (►Table 2). Long-term remissions were more frequent in newly diagnosed patients than in relapsing patients. Specifically, 15 of the 22 newly diagnosed patients who responded to first-line treatment (68.2%) achieved long-term remission, compared with only 6 of the 16 patients with relapsed ITP who initially responded (37.5%).

Regarding relapses, 7 out of the 22 newly diagnosed patients (31.8%) experienced a relapse after first-line treatment, while a higher proportion, 10 out of the 16 relapsed patients (62.5%), experienced another relapse. Interestingly, the newly diagnosed ITP patients had earlier relapses after a median (IQR) of 42 (15–90) days, compared with patients with relapsed ITP who relapsed after a median (IQR) time of 120 (23–390) days ($p = 0.04$; ►Table 2).

Subsequent Treatments to First-Line Therapy

►Fig. 1 presents a comprehensive overview of the treatment course in all patients. The eight patients who did not respond to first-line therapy were directly switched to second-line therapy. Of the 17 patients who relapsed after having responded to first-line treatment, 11 were switched to second-line therapy, while six received a second course of prednisolone.

Out of these six patients who received another cycle of corticosteroids, one achieved a long-lasting response, one was still undergoing treatment at the end of the observation period, and four were later switched to second-line therapy.

Overall, 23 patients (50.0%), 11 (40.7%) with newly diagnosed, and 12 (63.2%) with relapsed ITP, received second-line treatment. Of them, 8 were nonresponders to first-line treatment, 11 relapsed after treatment with corticosteroids, and 4 did not respond to another cycle of corticosteroids. Second-line therapies and response rates according to the groups are shown in ►Table 3.

Of the 23 patients receiving second-line treatment, 19 patients (82.6%) received TPO-RAs as second-line therapy, 1 (4.3%) received rituximab, and 3 (13.0%) underwent splenectomy. Although 100% of patients with newly diagnosed ITP received TPO-RA as a second-line treatment, 4 patients with relapsed ITP (33.3%) were treated with rituximab or splenectomy. The median (IQR) time between the start of first-line treatment and second-line treatment was 102 days (20–335), for newly diagnosed patients not significantly shorter (median: 87 days [14–202]) than for relapsed patients (median: 215 days [55–390], $p = 0.36$). Patients with newly diagnosed ITP had significantly lower platelet counts at the start of treatment ($p = 0.04$) than patients with chronic relapsed ITP.

Response to Treatment with TPO-RA

Of the 19 patients, who received TPO-RA as second-line treatment, 13 patients (68.4%) received eltrombopag, 4 patients (21.5%) received avatrombopag, and 2 patients (10.5%) received romiplostim (►Table 3). Overall, 14 patients responded to TPO-RA treatment resulting in an ORR to TPO-RAs of 73.7%, which was similar in newly diagnosed (72.7%) and relapsed ITP patients (75.5%). Also, the median time to OR was similar in newly diagnosed and relapsed patients. Five (26.3%) patients did not respond to TPO-RA treatment after a median (IQR) treatment duration of 39.6 (25–120) days. The majority of patients had no adverse effects with TPO-RA treatment. Only 2 of 19 patients (10.5%) reported headache and nausea as adverse effects.

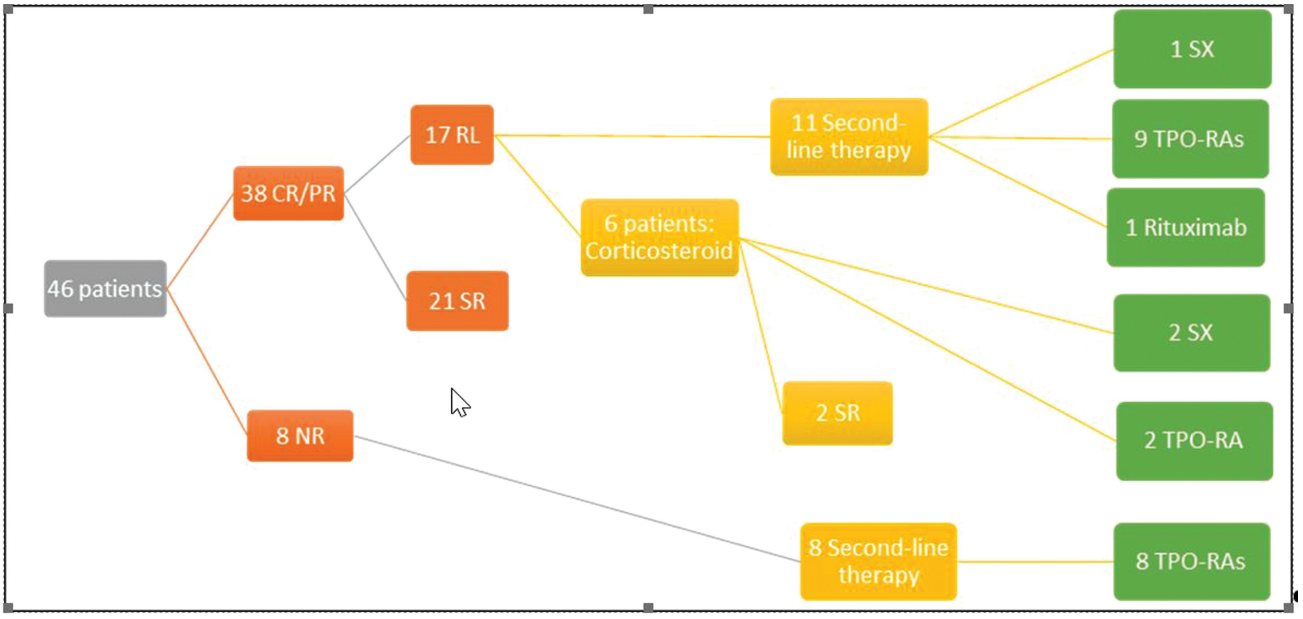

Fig. 1 Treatment strategies from first-line therapies to second-line therapies. CR, complete response; PR, partial response; NR, nonresponse; RL, relapse; SR, sustained response; TPO-Ras, thrombopoietin receptor agonist; SX, splenectomy.

Table 3 Outcome of second-line therapy of all patients ($n = 23$) and according to disease duration

	Primary ITP ($n = 23$)	Newly diagnosed ITP ($n = 11$)	Relapsed ITP ($n = 12$)	*p*
Time to switch to second-line treatment	102 (20–335)	87 (14–202)	215 (55–390)	0.36
Platelet count at the initiation of second-line therapy, $\times 10^9$/L, median (IQR)	20 (5–30)	11 (1–15)	28 (10–32)	0.04
TPO-RAs, *n* (%)	19 (82.6)	11 (100)	8 (66.7)	0.15
Eltrombopag, *n* (%)	13 (56.5)	8 (72.7)	5 (41.7)	–
Avatrombopag, *n* (%)	4 (17.4)	2 (18.2)	2 (16.6)	–
Romiplostim, *n* (%)	2 (8.7)	1 (9.1)	1 (8.3)	–
Splenectomy	3 (13.0)	0 (0)	3 (25)	–
Rituximab	1 (4.4)	0 (0)	1 (8.3)	–
Duration of treatment, median (IQR)	108 (35–285)	90 (35–192)	110 (45–285)	0.35
Response rates				
Response to TPO-RA treatment, ORR, *n* (%)	14 (73.7)	8 (72.2)	6 (75.5)	0.90
Time to response, days, median (IQR)	15 (12–20)	10 (8–15)	13(10–26)	0.80
CR, *n* (%)	10 (52.6)	7 (63.6)	3 (37.5)	0.10
Time to CR, days, median (IQR)	10 (8–35)	15 (5–40)	35 (10–45)	0.65
PR, *n* (%)	4 (36.8)	1 (9.1)	3 (37.5)	0.40
Time to PR, days, median (IQR)	18 (15–30)	13 (6–30)	19 (12–22)	0.59
NR, *n* (%)	5 (26.3)	3 (27.3)	2 (25.0)	0.86
Response to splenectomy				
CR, *n* (%)	2 (66.7)	NA (0)	2 (66.7)	–
NR, *n* (%)	1 (33.3)	NA(0)	1 (33.3)	–
Response to rituximab	NR		NR	–
Relapse after treatment				
Loss of R, *n* (%)	4 (23.5)	2 (25.0)	2 (33.3)	–
Time to loss of R, months median (IQR)	4.5 (2–6)	3 (2–45)	10 (6–14)	–

Abbreviations: CR, complete response; IQR, interquartile range; IQR, interquartile range; ITP, immune thrombocytopenia; *n*, number; NR, nonresponse; PR, partial response; R, response.

Other Second-Line Treatments

Four patients received no TPO-RAs. One of them received two cycles of rituximab (375 mg/m^2), but the treatment had to be stopped due to an adverse drug reaction. Splenectomy was performed in three patients. Splenectomized patients were followed up for a median (IQR) time of 48 (30–60) months. The median duration from diagnosis until splenectomy was 33 (12–50) months. Two patients achieved CR median time of 60 days after the splenectomy, the other patient had NR.

In summary, 7 patients (30.4%) had NR to second-line therapy (TPO-RA: $n = 5$, rituximab $n = 1$, splenectomy $n = 1$) and 4 of the 16 patients (25.0%) who were primarily responsive to second-line therapy (CR + PR) relapsed after a median (IQR) time of 4.5 (2.0–6.0) months. Seven of the responding patients (43.8%) achieved sustained remission to second-line therapy and did not require further lines of treatment in the median follow-up time of 2.4 years. For four patients (25.0%), treatment is still ongoing and one patient died of non–ITP-related death during the follow-up period.

Differences in Management According to Guidelines

During the prospective follow-up, the newly revised ITP Guidelines of the American Society of Hematology[7,10,14] in December 2019 with one major focus on the limitation of corticosteroid use to reduce toxicities.[14] Therefore, we additionally investigated the impact of the new guidelines on the management of our patients. Results are shown in ►Table 4.

Twenty-three patients (50.0%) had their first visit before the publication of the guidelines in 2019, while 23 patients (50.0%) had their first visit after the publication of the guidelines. The median (IQR) platelet count at treatment initiation was similar before and after the publication of the guidelines (10 (4–21) $\times 10^9$/L and 10 (4–17) $\times 10^9$/L), as was the rate of the administered treatments (prednisolone and prednisolone + IVIG). The median (IQR) duration of the first-line therapy showed a significant decrease from 100 days (56–242) before 2019 to 52 days (35–67) after the publication ($p = 0.01$). The median number of first-line therapies before switching to a second-line therapy decreased

Table 4 Differences in management before and after the publication of the ASH ITP guidelines in 2019

	Before 2019 ($n=23$)	After 2019 ($n=23$)	p
Newly diagnosed, *n* (%)	11 (47.8)	16 (69.6)	0.13
Relapsed, *n* (%)	12 (52.2)	7 (30.4)	0.13
Bleeding at inclusion, *n* (%)	16 (75.0)	15 (65.2)	0.64
Platelet count at inclusion, $\times 10^9$/L, median (IQR)	10 (4–21)	10 (4–17)	0.45
First-line therapy			
Prednisolone	15 (65.2)	16 (69.6)	–
Prednisolone + IVIG	8 (38.8)	7 (30.1)	–
Duration of first-line treatment, days, median (IQR)	100 (56–242)	52 (35–67)	0.01
Numbers of first-line therapies, median (IQR)	2 (1–3)	1 (1–2)	0.01
Time to switch to second-line therapy	160 (84–360)	47 (14–86)	0.01
Second-line therapy			
Number of patients, *n* (%)	15 (65.2)	8 (34.8)	0.02
TPO-RAs, *n* (%)	11 (73.8)	8 (100)	0.37
Rituximab, *n* (%)	1 (6.7)	0 (0)	0.31
Splenectomy, *n* (%)	3 (13.0)	0 (0)	0.07

Abbreviations: BS, bleeding score; CR, complete response; IQR, interquartile range; ITP, immune thrombocytopenia; *n*, number; NR, nonresponse; PR, partial response.

significantly from 2 to 1 ($p=0.01$), and the number of splenectomies during the observation period decreased from 3 before 2019 to 0 after 2019 ($p=0.31$). Correspondingly, the rate of TPO-RA as the second-line treatment increased from 73.8 to 100%. Furthermore, data showed an earlier switch to second-line treatment, as the median time until the switch to second-line therapy significantly decreased from 160 (84–360) days to 47 (14–86) days, $p=0.01$.

Discussion

The treatment of ITP patients varies in terms of used therapies and treatment sequence according to the availability of treatments, the experience of the treating physicians, and the patient's preferences. In our substudy of the Vienna ITP Biobank, we provide a structured and prospective analysis of administered treatments and their efficacy and tolerability in 46 adult patients with acute primary ITP in Austria. All patients received prednisolone as the first-line corticosteroid with a high ORR of over 82%. Nevertheless, sustained responses were only achieved by 21 patients (45.6%). The most common second-line treatment was TPO-RA, started after a median time of 98 days. Furthermore, we analyzed the impact of international guidelines[7,14] on the clinical practice of ITP treatment in Austria, which revealed an earlier switch to second-line treatment, and the more common use of TPO-RA as second-line treatment in all patients after 2019.

The clinical characteristics of our study are in line with previous data with respect to age and sex, showing a higher prevalence of females and a median age of 43 years. Our cohort includes a wide age range, from very young patients aged 18 years to elderly patients with a maximum age of 88 years, demonstrating similar age distribution to other studies.[3,16–18] Additionally, the platelet count at the initiation of first-line treatment reflects the common recommendations, as 91.3% of our ITP patients had a low platelet count below 30×10^9/L and 67.4% had bleeding symptoms.

All patients received prednisolone as the first-line corticosteroid. The guidelines recommend both prednisolone and dexamethasone as treatment options. However, ASH specifically recommends dexamethasone if a rapid increase in platelet count is desired.[14] Over 82% of our patients responded to corticosteroid treatment, in line with previously reported response rates of 60 to 80%.[19–21] Overall, the median duration of corticosteroid treatment was 8.8 weeks, and thus exceeded the short-term therapy with prednisone of less than 6 to 12 weeks which is suggested in the current guidelines.[6,7,14,22] Nevertheless, in the separate analysis of treatment duration before and after the publication of this recommendation, we can show a relevant shortening of the treatment time from 14 weeks before December 2019 to 7 weeks thereafter. This reflects the efficient implementation of international guidelines and treatment practices in our center.

In line with previous reports,[19,21–24] 37% of patients who initially responded to corticosteroids lost their response when the treatment was tapered and stopped. This underlines the limited potential of corticosteroids to induce long-term remissions. Of note, more patients with newly diagnosed than relapsed ITP achieved long-term remissions, but newly diagnosed patients had a shortened duration of response with earlier relapses than those with relapsed ITP. It should be mentioned that this is likely due to the natural history of ITP rather than the effect of corticosteroids.

According to the guidelines and due to good availability in Austria, TPO-RAs were the most common second-line treatment. Unlike treatment with prednisolone, TPO-RAs were well tolerated and only a few patients experienced known side effects such as headache during the treatment.[25–27] Our patients showed a high initial response rate of 73.7% with an equal ORR in newly diagnosed than in relapsed ITP patients. These response rates are similar to those in chronic ITP patients,[27–30] although treatment was already initiated in the phase of persistent ITP. Of note, the rates of CRs to TPO-RA treatment were higher in newly diagnosed than in relapsed ITP. This points toward a certain proportion of patients who might benefit from immunosuppressive rather than thrombopoiesis-stimulating agents in both groups, newly diagnosed and relapsed ITP patients. According to previous data, the time to response to TPO-RA treatment usually requires 12 to 20 days,[31] which is in line with our findings.

Our real-world data show an early use of TPO-RA at our center, as these treatments were already initiated after 87 days in newly diagnosed ITP patients. This underlines the current regional recommendations, which recommend the early use of TPO-RA after corticosteroid failure or early relapse after the initial response.[27] Even before 2019, we used TPO-RA early on, including in newly diagnosed patients, despite their approval only for treatment in the chronic phase after splenectomy or after 6 months of disease duration at that time. Second-line therapy with romiplostim, eltrombopag, and avatrombopag has a high efficacy and safety in adult ITP patients.[32,33] Although new therapies for ITP are available, according to our data and data from the literature,[34] there is only a minority of patients who do not respond to multiple lines of treatment.[21,32] Nevertheless, 13% of the patients analyzed in our cohort had NR to first-line corticosteroids and second-line treatment. Furthermore, the economic burden of ITP treatment is increasing with the introduction of novel therapies. The earlier use of TPO-RA might lead to additional treatment costs, as patients treated with TPO-RA continue to experience significant complications, such as infections, thromboembolic events, and bleeding incidents, which often require emergency treatments. Consequently, while these newer treatments offer therapeutic benefits, they also contribute to the overall economic strain on healthcare systems due to the additional management required for these adverse events.[18,35,36]

Rituximab has also been recommended as second-line therapy in international guidelines.[37–39] In the current study, only one patient received rituximab as a second-line therapy after corticosteroid failure. In general, rituximab is well tolerated,[40] but our patient developed an adverse treatment reaction, which led to treatment discontinuation. Two other patients received rituximab as a subsequent treatment line after nonresponse to TPO-RAs during the study and both achieved CR after a median period of 12 days.

The ASH guidelines and others still recommend splenectomy as a second-line therapy for relapsed or refractory chronic ITP, because of its high rate of long-term remissions.[41] Only three patients underwent splenectomy in our study, of which two achieved CR while one showed NR. These results of our study are very similar to the remission rates described in the literature.[41] However, in line with international developments, the number of splenectomies significantly decreased also in Austria, not least because of the introduction of new well-tolerated and noninvasive treatments.[42] Splenectomy is an invasive procedure and is associated with an increased lifetime risk of infections, malignancy, and venous thrombosis.[3,43,44] This has led physicians to avoid or delay performing the procedure. In line, no patient in our study population has undergone splenectomy since 2019.

Furthermore, our prospective data could show a high impact of new guidelines in 2019 on the treatment of our patients, resulting in the early switch to second-line treatment, underlined by reduced numbers of corticosteroid cycles prior to second-line treatment, as well as a shortened duration until second-line therapy. This is in line with other retrospective data showing an overuse of corticosteroids in the past and historical overuse of corticosteroids and a current preference for earlier initiation of TPO RA.[13,27,45]

This real-world study has some limitations. This study was observational, which means treatment decisions were made at the discretion of physicians. Furthermore, data on side effects and causes for treatment changes were not systematically recorded in questionnaires, but during clinical routine. Since this study is based on real-world data and lacks multivariate analysis, there may be confounding factors influencing the results. Consequently, the statistical comparisons between patient groups should be interpreted carefully.

Patients with relapsed ITP reported in this study represent a selection of patients who might have previously been responsive to corticosteroids and thus were again treated with corticosteroids. Thus, these response data might not be applicable to all patients with relapsed ITP. Lastly, there was a variation in the individual follow-up time which ranged from 3 to 78 months. Nevertheless, the observation period was over 2 years in 80% of cases, which also can be seen as strength of the study, as this long observation period allows for a comprehensive analysis of the data and increases the reliability of the study results. Moreover, the use of standardized definitions and terms in our study ensures comparability with other studies worldwide.[15] The Vienna ITP Biobank is the largest prospective collection of adult patients with primary ITP in Austria. This analysis offers novel insights into the epidemiology, clinical management, and treatment of adult patients with ITP in Austria.

Conclusion

Response rates to first-line treatment with corticosteroids in newly diagnosed or relapsed ITP patients are in line with previous data. Nevertheless, only 50% achieve sustained remission of first-line treatment. TPO-RAs are the most commonly used second-line therapy and appear to be well-tolerated and effective. The implementation of international guidelines has led to a faster switch to second-line therapy and more common use of TPO-RAs as second-line therapy, and the rate of splenectomies has significantly

decreased. Since this study lacks multivariate analysis, confounding factors may influence the results, so comparisons should be interpreted carefully. We conclude that the integration of real-life experience, expert consensus papers, and international guidelines optimizes the management and treatment of ITP patients.

What Is Known About This Topic?

- The treatment of ITP patients varies in terms of used therapies and treatment sequence.
- According to the availability of treatments, experience of the treating physicians, and patient's preferences.

What Does This Paper Add?

- Offers novel insights into the epidemiology, clinical management, and treatment strategy of adult patients with ITP in Austria.
- Its evolution in light of the changes in international guidelines.

Authors' Contributions

All authors contributed to the study's conception and design. Data collection was performed by J.R., T.S., D.M., and M.F. Data analysis was performed by J.R. and T.S. The first draft of the manuscript was written by J.R.; I.P. and J.G. commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. D.M. received honoraria for advisory board meetings and lectures from CSL Behring. I.P. received a grant from CSL Behring for the Medical University of Vienna; honoraria from CSL Behring, Sobi, Takeda, and Pfizer for lectures and advisory board meetings; as well as travel support by Sobi. T.D. and V.N-N. are employees of Novartis. C.A. received honoraria from Bayer, CSL Behring, Novo Nordisk, Pfizer, Roche, Sobi, and Takeda for lectures and participation in advisory board meetings. J.G. received honoraria for lectures and advisory board meetings and research funding for the Medical University of Vienna from CSL Behring, Novartis, Amgen, and Sobi. J.R., T.S., and M.F. have no conflicts of interest.

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