Switching between eltrombopag and recombinant human thrombopoietin in patients with immune thrombocytopenia: an observational study

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Background: Recombinant human thrombopoietin (rh-TPO) and eltrombopag are two distinct TPO receptor agonists (TPO-RAs) with different mechanisms. During the pandemic, when immunosuppressive medications are controversial, switching to another TPO-RA may be worth exploring in patients who do not benefit from their first TPO-RA. We investigated the outcomes of switching from rh-TPO to eltrombopag or vice versa in immune thrombocytopenia (ITP) patients.

Methods: This prospective, open-label, observational investigation included 96 adult ITP patients who needed to switch between rh-TPO and eltrombopag between January 2020 and January 2021 at Peking University People's Hospital in China. The study evaluated response rates and platelet counts at different time points after the switch, bleeding events, time to response, duration of response, and adverse events.

Results: At 6 weeks after switching, response was observed in 21/49 patients (43%) who switched for inefficacy and 34/47 patients (72%) who switched for non-efficacy-related issues. In the inefficacy group, 9/27 patients (33%) responded to eltrombopag, and 12/22 patients (55%) responded to rh-TPO. In the non-efficacy-related group, 21/26 (81%) and 13/21 (62%) patients in the eltrombopag and rh-TPO groups maintained their response rates at 6 weeks after switching, respectively. Response at 6 months was achieved in 24/49 patients (49%) switching for inefficacy and 37/47 patients (79%) switching for non-efficacy issues. In the inefficacy group, 13/27 patients (48%) responded to eltrombopag, and 11/22 patients (50%) responded to rh-TPO. In the non-efficacy-related group, 22/26 patients (85%) and 15/21 patients (71%) in the eltrombopag and rh-TPO groups maintained their response rates at 6 months after switching, respectively. Both eltrombopag and rh-TPO were well tolerated.

Conclusions: Our study confirmed the safety and effectiveness of switching between rh-TPO and eltrombopag for ITP patients who had no response to or experienced adverse events with their first TPO-RA. When the switch was motivated by other reasons, including patient preference and platelet count fluctuations, the probability of response was high.

Registration: ClinicalTrials.gov, NCT04214951.

Keywords: Immune thrombocytopenia; Treatment switching; Treatment outcome; Eltrombopag; Thrombopoietin

Introduction

Although immunosuppressive strategies appear to be effective for immune thrombocytopenia (ITP) patients, the increasing risk of coronavirus infection has been a substantial challenge during the pandemic.[1,2] Non-immunosuppressive treatments such as thrombopoietin (TPO) agents would allow for possible tapering and even discontinuation of these immunosuppressant medications. Recombinant human thrombopoietin (rh-TPO, brand name Tebiao) and eltrombopag are two distinct TPO receptor agonists (TPO-RAs) with different mechanisms of action and thus different response and safety profiles.[3,4] The price for eltrombopag is lower than rh-TPO in China for the 2-week treatment period, and romiplostim is still unavailable in China. Although rh-TPO and eltrombopag have promising therapeutic effects and relatively low toxicity, some patients do not benefit from their first TPO-RA due to inefficacy or intolerance.[5,6] Under the coronavirus disease 2019 (COVID-19) pandemic, when immunosuppressive medications are controversial, switching to another TPO-RA may be worth exploring among these ITP patients before initiating immunosuppressant

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medications. However, few data exist to directly evaluate the outcomes of sequential treatments with eltrombopag and rh-TPO in clinical practice. Therefore, we proposed a prospective observational study of ITP patients for whom a switching strategy from rh-TPO to eltrombopag or vice versa was planned. The effectiveness and safety of switching for various reasons in actual clinical practice were assessed.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Institutional Review Board of Peking University People's Hospital (No. 2019PHB269-01). Informed written consent was obtained from all patients prior to their enrollment in this study. This study was registered at ClinicalTrials.gov (NCT04214951).

Study design

Individuals were screened for eligibility for the study if they switched from rh-TPO to eltrombopag or vice versa between January 2020 and January 2021 in our hospital. ITP patients who switched between rh-TPO and eltrombopag were enrolled at the time of switching [Supplementary Figure 1, http://links.lww.com/CM9/B203]. Patients switching from eltrombopag to rh-TPO were the rh-TPO group, whereas patients switching from rh-TPO to eltrombopag were the eltrombopag group. The complete inclusion and exclusion criteria are presented in Table 1. After a 2-week wash-out period, patients were followed up prospectively upon administering the second TPO-RA. After-switch rh-TPO and eltrombopag were applied according to the approved label and clinical practice, considering the actual conditions of the patient (explain detailed in Supplementary Methods, http://links.lww.com/CM9/B203).

Patients were followed up for at least 6 months after switching. In patients who switched from rh-TPO to eltrombopag, platelet counts were obtained weekly under a stable dose and monthly following the establishment of a stable platelet count ($\geq 50 \times 10^9$/L for > 4 weeks), while platelet counts were obtained at least once a week during dose adjustment. Liver function tests were performed monthly under a stable dose but increased to biweekly during dose adjustment. For patients who switched from eltrombopag to rh-TPO, platelet counts were obtained every other day during initial treatment and biweekly during maintenance therapy. Platelet counts were obtained at least biweekly for patients who suspended their second TPO-RA due to response. Once treatment was resumed, monitoring of platelet counts and liver function was performed as described during treatment administration.

Reasons for the switch

Reasons for switching were grouped into two categories: lack of efficacy with the first TPO-RA and non-efficacy-related issues. Non-efficacy-related reasons included patient preference, platelet count fluctuations, and adverse events.[7,8] Platelet count fluctuation is empirically defined as more than two weekly platelet counts $< 30 \times 10^9$/L or $> 400 \times 10^9$/L in a month and a change of $> 200 \times 10^9$/L in weekly platelet counts.[7-9]

Outcome measures

The primary endpoint evaluated the response rate at 6 weeks after switching for different reasons. Secondary endpoints included platelet counts and response rates at different time points after the switch, bleeding events, time to response, duration of response, and adverse events.

Table 1: Full inclusion and exclusion criteria.

Inclusion criteria	All the following conditions must apply to the prospective patient at screening: • Age ≥18 years • Primary ITP[13,22] • Switch from rh-TPO to eltrombopag or vice versa • Insufficient response or relapse after prior ITP treatments • Available follow-up for at least 6 months after switch • WOCBP willing to use highly effective contraceptive measures during the study period • Concomitant ITP regimens were permitted if the doses were stable for > 4 weeks before switch
Exclusion criteria	Patients will be excluded from the study if they meet any of the following criteria: • HIV-positive status or active infection with HBV or HCV • History of thrombosis • Lactating or pregnant women or WOCBP unwilling to use contraceptive measures • Abnormal liver and renal functions: AST or ALT ≥3 ULN, and/or total bilirubin ≥1.5 ULN, and/or creatinine ≥176.8 μmol/L • Suffering from serious diseases that the investigators consider inappropriate for enrollment {i.e., cancer or precancer, immunecompromised, uncontrolled diabetes, epilepsy, and severe cardio-cerebrovascular diseases (i.e., stroke, idiopathic aortic stenosis, aneurysm, hypertrophic obstructive cardiomyopathy, ischemic heart disease, tachyarrhythmias, severe heart failure [classified as NYHA III–IV], severe lung dysfunctions, and etc.)}

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; ITP: Immune thrombocytopenia; NYHA: New York Heart Association Classification; rh-TPO: Recombinant human thrombopoietin; ULN: Upper limit of normal; WOCBP: Women of childbearing potential.

Statistical analysis

This observational study aimed to describe the efficacy of each TPO-RA after switching for various reasons in actual clinical practice. As a result, we enrolled consecutive ITP patients throughout the whole year at Peking University People's Hospital to reduce recruitment bias. All patients who received at least one dose of the second TPO-RA, except for those who withdrew consent, were included in the primary assessment. All patients who received at least one dose of the second TPO-RA were included in the safety analysis. Patients who discontinued their second TPO-RA except for response were considered as nonresponse and the analysis of primary and secondary endpoints was performed by imputing missing values as failures. Categorical variables were described as counts with percentages. Continuous variables were described as means and standard deviations if the data followed a normal distribution; otherwise, the data were described as medians with interquartile ranges. Pearson χ^2 and Fisher's exact tests were used to compare the qualitative data, and odds ratios with 95% confidence intervals were calculated with logistic regression analysis. Quantitative data were compared using Student's *t* test when the data followed a normal distribution; otherwise, the Mann-Whitney *U* test was used. Time-to-event data were analyzed using Kaplan-Meier survival curves with log-rank tests for between-group comparisons, including duration of response, time to relapse, and time to response. Unless otherwise specified, statistical testing was conducted bilaterally with values of $P < 0.05$. Statistical analyses were computed with SPSS version 24 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism version 7 (GraphPad Software, San Diego, USA).

Results

Patients

Between January 2020 and January 2021, 158 patients were screened for eligibility [Figure 1]. After screening for eligibility, 56 patients who switched from rh-TPO to eltrombopag and 50 patients who switched from eltrombopag to rh-TPO were enrolled in our study at the time of switching. During the 6-month follow-up, three patients in the eltrombopag group and seven in the rh-TPO group dropped out from the study due to consent withdrawal; and four patients in the eltrombopag group and three in the rh-TPO group were lost to follow-up.

A total of 63 female and 33 male patients were enrolled in this study. The median age was 43 years when they switched to the second TPO-RA. The disease duration before switching was highly variable, ranging from 1 month to approximately 40 years. The baseline characteristics of the enrolled subjects were comparable between the eltrombopag and rh-TPO groups, except for age [Table 2].

Reasons for the switch

The reasons for switching included lack of efficacy with the first TPO-RA and non-efficacy-related issues [Table 2]. Non-efficacy-related reasons included patient preference

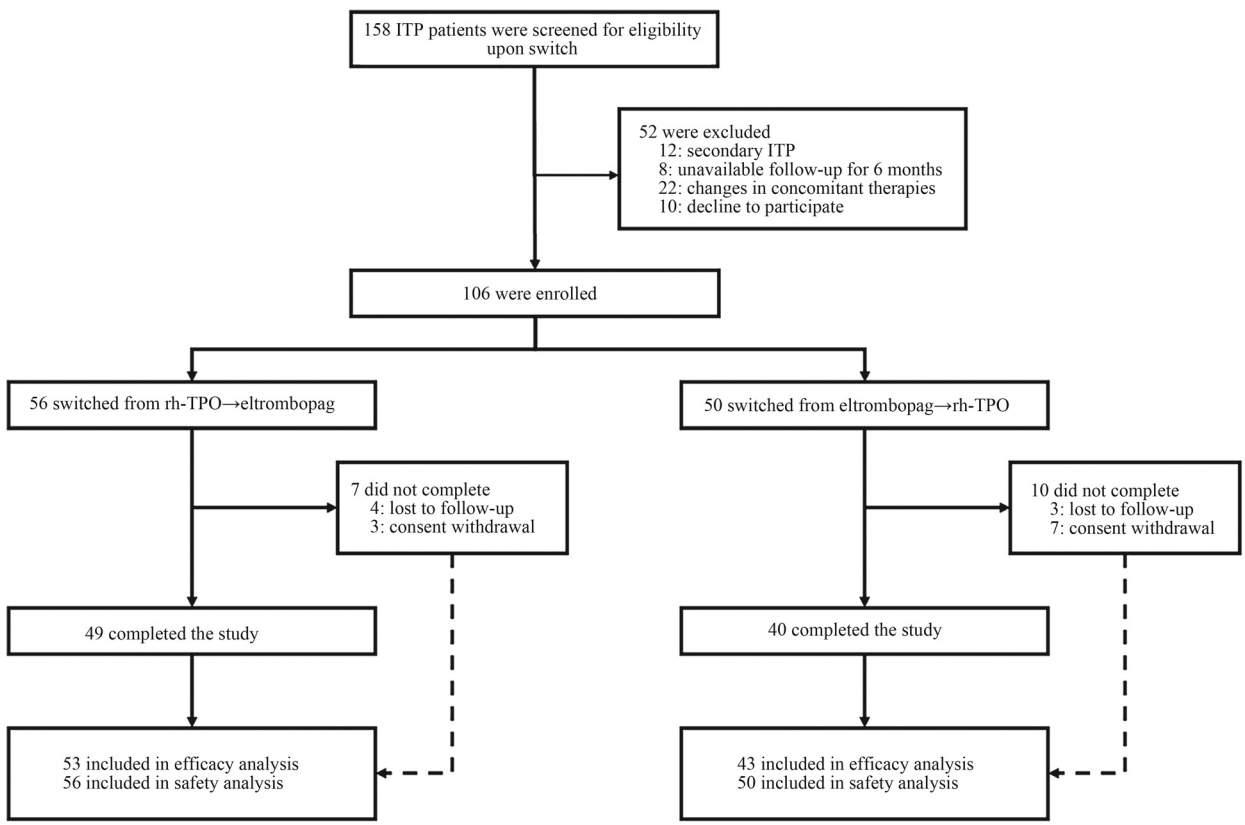

Figure 1: Cohort flow of the study. ITP: Immune thrombocytopenia; rh-TPO: Recombinant human thrombopoietin.

(21 patients, 22%), platelet count fluctuations (13 patients, 14%), and adverse events (13 patients, 14%). Reasons for the switch differed between the eltrombopag and rh-TPO groups. Patients switched from eltrombopag to rh-TPO mainly due to eltrombopag's side effects, while eltrombopag was preferred on account of the oral administration route.

Outcomes of patients in the inefficacy group

The outcomes of patients switching for inefficacy with the first TPO-RA were detailed in Table 3. Response rates at 6 weeks after switching (the primary endpoint) were observed in 21 patients (43%) who switched for

Table 2: Baseline characteristics of adult ITP patients who needed to switch between rh-TPO and eltrombopag at the time of switching.

Characteristics	Total ($n=96$)	Eltrombopag group ($n=53$)	Rh-TPO group ($n=43$)	t/χ^2	*P*-value
Age (years), mean ± SD	45.3 ± 18.3	48.9 ± 18.1	40.8 ± 17.8	2.187	0.03*
Gender, *n* (%)				1.444	0.23†
Male	33 (34)	21 (40)	12 (28)		
Female	63 (66)	32 (60)	31 (72)		
Type of ITP, *n* (%)				4.314	0.12†
Newly diagnosed	16 (17)	11 (21)	5 (12)		
Persistent	12 (13)	9 (17)	3 (7)		
Chronic	68 (71)	33 (62)	35 (81)		
Time from switch to diagnosis (months), mean ± SD	51.5 (7.0–95.8)	58.0 (3.0–96.5)	38.0 (14.0–90.0)	–0.741	0.46§
Hemoglobin on switch (g/L), mean ± SD	130.3 ± 20.4	129.7 ± 23.3	131.1 ± 16.3	–0.356	0.72*
White blood cells ($\times10^9$/L) on switch, mean ± SD	7.9 ± 2.7	8.1 ± 3.0	7.6 ± 2.4	0.817	0.42*
Splenectomy, *n* (%)	3 (3)	1 (2)	2 (5)	–	0.59‡
Reasons for the switch				9.176	0.03†
Lack of efficacy, *n* (%)	49 (51)	27 (51)	22 (51)		
Non-efficacy-related issues, *n* (%)					
Patient preference	21 (22)	16 (30)	5 (12)		
Platelet count fluctuations	13 (14)	7 (13)	6 (14)		
Side effects of the first TPO-RA	13 (14)	3 (6)	10 (23)		
Concomitant therapy with the second TPO-RA				–	–
Glucocorticoids, *n* (%)	63 (66)	31 (58)	32 (74)		
IVIg, *n* (%)	12 (13)	4 (8)	8 (19)		
Splenectomy, *n*	0	0	0		
Cyclosporin, *n*	33 (34)	16 (30)	17 (40)		
Mycophenolate mofetil, *n*	18 (19)	10 (19)	8 (19)		
Azathioprine, *n*	0	0	0		
Cyclophosphamide, *n*	0	0	0		
Rituximab, *n*	0	0	0		

* Student's *t* test. † Pearson χ^2 test. ‡ Fisher's exact test. § Mann–Whitney *U* test. ITP: Immune thrombocytopenia; IVIg: Intravenous immunoglobulin; rh-TPO: Recombinant human thrombopoietin; TPO-RA: Thrombopoietin receptor agonist. –: Not applicable.

Table 3: Response rates at different time points after switching.

Items			Total	Eltrombopag group	Rh-TPO group	χ^2	*P*-value
The inefficacy group			*N* = 49	*N* = 27	*N* = 22		
	6 weeks	CR+R, *n* (%)	13+8 (43%)	7+2 (33%)	6+6 (55%)	2.227	0.14*
		NR, *n* (%)	28 (57%)	18 (67%)	10 (45%)		
	3 months	CR+R, *n* (%)	12+10 (45%)	9+3 (44%)	3+7 (45%)	0.005	0.94*
		NR, *n* (%)	27 (55%)	15 (56%)	12 (55%)		
	6 months	CR+R, *n* (%)	13+11 (49%)	9+4 (48%)	4+7 (50%)	0.017	0.90*
		NR, *n* (%)	25 (51%)	14 (52%)	11 (50%)		
The non-efficacy-related group			*N*=47	*N*=26	*N*=21		
	6 weeks	CR+R, *n* (%)	16+18 (72%)	14+7 (81%)	2+11 (62%)	2.066	0.15*
		NR, *n* (%)	13 (28%)	5 (19%)	8 (38%)		
	3 months	CR+R, *n* (%)	20+18 (81%)	17+5 (85%)	3+13 (76%)	–	0.49†
		NR, *n* (%)	9 (19%)	4 (15%)	5 (24%)		
	6 months	CR+R, *n* (%)	18+19 (79%)	16+6 (85%)	2+13 (71%)	–	0.31†
		NR, *n* (%)	10 (21%)	4 (15%)	6 (29%)		

* Pearson χ^2 test. † Fisher's exact test. CR: Complete response; NR: Nonresponse; R: Response; rh-TPO: Recombinant human thrombopoietin.

inefficacy. Among them, nine of 27 patients (33%) responded to eltrombopag (complete response [CR] in seven patients, 26%), and 12 of 22 patients (55%) responded to rh-TPO (CR in six patients, 27%). At 6 months after switching, 13 of 27 patients (48%) responded to eltrombopag (CR in nine patients, 33%), and 11 of 22 patients (50%) responded to rh-TPO (CR in four patients, 18%). The response rate was comparable at different time points after switching between the eltrombopag and rh-TPO groups.

Platelet counts that significantly increased in both groups after switching were also comparable between the two groups at most subsequent assessments [Figure 2A]. No differences in time to response [Figure 2B] or duration of response [Figure 2C] were observed between the eltrombopag and rh-TPO groups.

Among patients in the eltrombopag group, the incidence of any bleeding symptoms (World Health Organization [WHO] grades 1–4) and clinically significant bleeding (WHO grades 2–4) decreased without reaching statistical significance after switching [Supplementary Table 1, http://links.lww.com/CM9/B203]. Among patients in the rh-TPO group, the incidence of any bleeding symptoms decreased significantly after switching. By contrast, the incidence of clinically significant bleeding decreased without reaching statistical significance after switching [Supplementary Table 1, http://links.lww.com/CM9/B203].

Outcomes of patients in the non-efficacy-related group

The outcomes of patients in the non-efficacy-related group were detailed in Table 3. Response rates at 6 weeks were observed in 34 patients (72%) who switched for non-efficacy-related issues. Among them, 21 patients (81%) in the eltrombopag group and 13 patients (62%) in the rh-TPO groups maintained their response rates at 6 weeks after switching, respectively. At 6 months after switching, 22 patients (85%) in the eltrombopag group and 15 patients (71%) in the rh-TPO group maintained their response rates in the non-efficacy-related group. The response rates were comparable at different time points after switching between the eltrombopag and rh-TPO groups. The response rates of different subgroups were detailed in Supplementary Figures 2 and 3, http://links.lww.com/CM9/B203.

Baseline platelets were 95×10^9/L in the eltrombopag group, which was far higher than the rh-TPO group (50×10^9/L). Platelet counts also increased in both groups after switching, and the increase from baseline was comparable [Figure 3A]. However, patients in the eltrombopag group had higher platelet counts at most assessments after switching due to higher baseline values. Similarly, fewer patients in this group relapsed after switching [Figure 3B]. Likewise, the duration of response in the rh-TPO group was shorter than that in the eltrombopag group [Figure 3C].

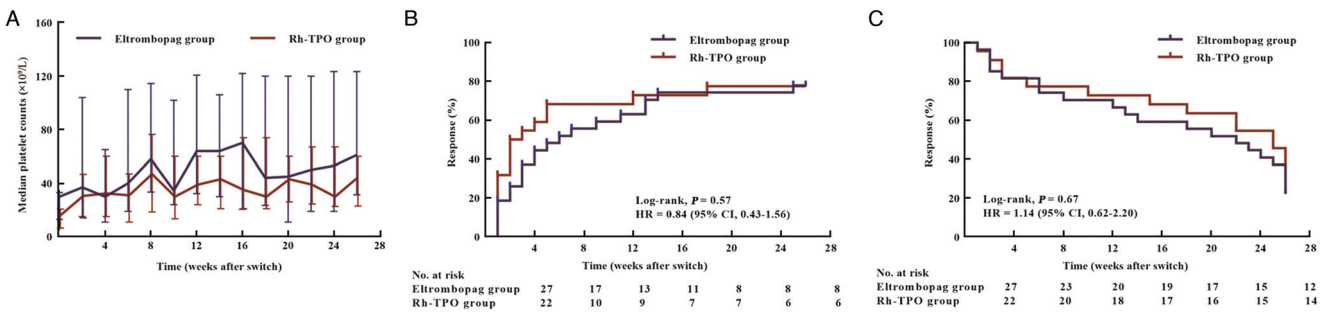

Figure 2: Outcomes of patients switching for inefficacy. (A) Median platelet counts in rh-TPO and eltrombopag group after switch. Error bars are IQRs. (B) Comparison of the time to response after switching between rh-TPO and eltrombopag groups. (C) Comparison of the duration of response after switching between rh-TPO and eltrombopag groups. CI: Confidence interval; HR: Hazard ratio; IQRs: Interquartile ranges; rh-TPO: Recombinant human thrombopoietin.

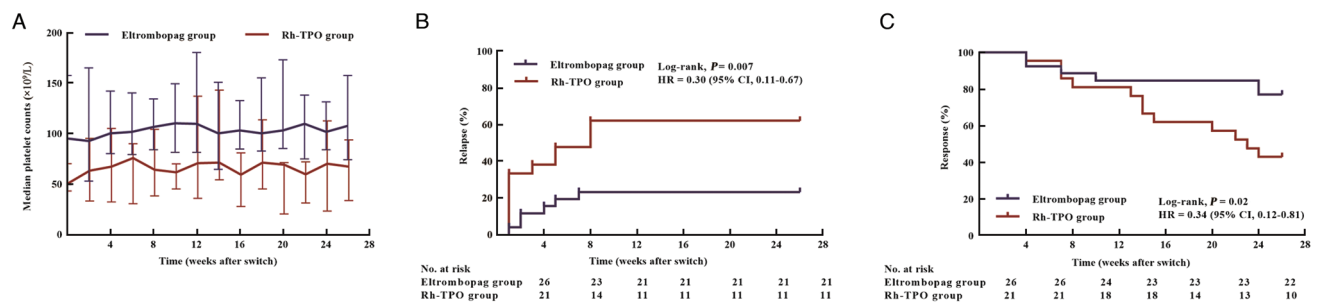

Figure 3: Outcomes of patients switching for non-efficacy-related issues. (A) Median platelet counts in rh-TPO and eltrombopag groups after switch. Error bars are IQRs. (B) Comparison of the time to relapse after switching between rh-TPO and eltrombopag groups. (C) Comparison of the duration of response after switching between rh-TPO and eltrombopag groups. CI: Confidence interval; HR: Hazard ratio; IQRs: Interquartile ranges; rh-TPO: Recombinant human thrombopoietin.

Adverse events

Thirteen patients developed clinical symptoms or laboratory abnormalities that led to the discontinuation of the first TPO-RA [Supplementary Table 2, http://links.lww.com/CM9/B203]. Among them, ten patients switched from eltrombopag to rh-TPO, and three switched in the opposite direction. Most adverse events resolved spontaneously after switching (11 patients, 85%).

Both after-switch treatments were well tolerated, and all the adverse events were grade 1–2. The incidence of adverse events was 18% (10/56) for patients receiving eltrombopag and 14% (7/50) for rh-TPO [Supplementary Table 3, http://links.lww.com/CM9/B203]. The most frequent adverse events were hepatotoxicity with eltrombopag, and dizziness and injection site reaction with rh-TPO. No serious adverse effects developed during the 6-month period, and no patients suspended treatments with the second TPO-RA due to side effects. Remarkably, no patients in our study were diagnosed with COVID-19 during the follow-up period.

Discussion

ITP patients are at a higher risk of infection because of the underlying disease and corresponding treatments.[10] To date, there have been few studies reporting the clinical course of ITP patients during the COVID-19 pandemic. Current guidance is to avoid immunosuppressive strategies or keep the dose and duration to the minimum. In addition to inhibiting platelet destruction, another therapeutic approach is to enhance thrombopoiesis through the TPO pathway.[11]

TPO-RAs have been shown to have high effectiveness and great tolerability in ITP patients.[12] However, some patients do not benefit from their first TPO-RA due to inefficacy or intolerance.[5] There is a misconception that, if one TPO-RA fails, so does the other TPO-RA. However, clinical sequential therapy with romiplostim and eltrombopag provides favorable outcomes and tolerance.[13] Therefore, when inefficacy or adverse events occur with one TPO-RA, switching to another TPO-RA may be a sound decision.[13,14] Unfortunately, previous researches almost exclusively focused on the switch between romiplostim and eltrombopag, and all findings were obtained from retrospective studies. Likewise, rh-TPO and eltrombopag have distinct molecular structures, treatment mechanisms, and pharmacokinetic characteristics and thus different response patterns and side effect profile.[14-17] We prospectively explored the switching between rh-TPO and eltrombopag, hoping to provide more rational suggestions for the management of ITP patients during the pandemic. The 2-week washout period before initiation of the subsequent therapy was set to minimize possible effects of the prior treatment in our design.

There are several reasons for switching treatments in ITP patients, and the outcomes varied in different groups. Consistent with other series, our results showed that inefficacy was the main reason for switching.[9] When the reason was lack of efficacy with the first TPO-RA, response rates with the second TPO-RA ranged from 45% to 80%.[7,9,14] Notably, both eltrombopag and rh-TPO achieved good outcomes as the second treatment in our study. Platelet count fluctuations with TPO-RAs have been reported previously, although the precise mechanism remains poorly understood.[9,18] A matter of concern was the increasing risk of bleeding or thrombocytosis.[19,20] Previous reports showed that more patients switched from romiplostim to eltrombopag for this reason than in the other direction.[7,9,14] However, in our report, a comparable incidence was observed in the two sequences. Consistent with previous findings, the fluctuation resolved in most patients after switching.[17] An alternate TPO-RA should be considered for patients with severe adverse events, as eltrombopag and rh-TPO have nonoverlapping tolerance profiles.[7,9,14] In line with previous findings, most patients in our study who switched due to intolerance responded to the second TPO-RA. Additionally, no severe side effects were reported after switching, and no patients suspended the second TPO-RA due to side effects. Patients appeared to favor eltrombopag over rh-TPO due to easier administration routes.[7,9,14] Against the backdrop of COVID-19, unnecessary visits to clinics should be limited to minimize the risk of viral transmission. Remarkably, no patient was diagnosed with COVID-19 during the follow-up in the present study. Almost all individuals could maintain the response after switching due to their preference.[9,14]

Overall, a tendency toward better response appeared to occur in patients switching from rh-TPO to eltrombopag in the present study. The primary explanation might be that patients in the rh-TPO group had lower baseline platelet counts, indicating that they had more severe ITP and logically leading to worse outcomes. Indeed, if we considered the increase in platelet counts from baseline and the resolution of hemorrhage, the two sequences were comparably effective.

The primary limitation of this study was the single-center analysis with a limited sample size and potential selection bias, which might limit the generalizability of our results. The real-world observational data from the survey-based approach could not ensure that all possible patients were enrolled or that all data were recorded at the appointed time. Other limitations included the heterogeneous medical history of these patients at the time of switching and the relatively short follow-up time. Further confirmation in large-scale studies is warranted.

Our future research direction is to enroll patients when they begin to use TPO-RAs. We will randomize enrolled patients to eltrombopag or rh-TPO and follow them. Patients who cannot benefit from their first TPO-RA due to various causes will be switched to the other TPO-RA. The outcomes after switching will be recorded. In this way, we will better understand the influence of the first TPO-RA on the outcomes after switching.

The management for ITP patients should be individualized based on the risk of hemorrhage and the exposure to SARS-CoV-2 infection. In the present study, we reported the clinical course of ITP patients with TPO-RAs during

COVID-19, which is different from the treatments before the pandemic. The previously commonly used treatments for chronic or relapsed ITP patients were immunosuppressant drugs. However, treatments that are not immunosuppressive, such as intravenous immunoglobulin and TPO agents, are our first choices at present. Considering the frequently changing conditions, guidance on how to deal with ITP needs to be updated in time.[21] More data are urgently needed to form the optimal management of ITP during the pandemic.

In conclusion, when no response is achieved with the first TPO-RA, it is worth trying to switch to the other TPO-RA. The safety profiles of the two available TPO-RAs do not completely overlap. Therefore, if patients experience adverse events with the first TPO-RA, switching TPO-RAs may be effective and safe. In other cases, when patients switch for other reasons, including patient preference and platelet count fluctuations, there is a high probability of responding to the second TPO-RA. Our findings may provide a promising strategy for the treatment of ITP.

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Conflicts of interest

None.

Data availability statement

Deidentified individual participant data will be available from the publication date by contacting Dr. Xiaohui Zhang (E-Mail: zhangxh@bjmu.edu.cn).

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