LPV/r was suspended due to possible interactions. During follow-up, we identified a progressive platelet count increase (Fig. 1), which was assessed at the pharmacovigilance institutional center as a suspected adverse drug reaction related to ruxolitinib, based on the temporality of the platelet count rise and the duration of the ruxolitinib effect. After stopping ruxolitinib, the platelet count decreased and normalized, and interleukin-6 levels decreased until they were undetectable on day 13 after ruxolitinib, without relevant changes in the rest of the inflammatory markers. We administered an anticoagulation treatment with enoxaparin 80 mg SC BID, maintaining anti-Xa therapeutic levels, and the patient was discharged without clinical complications.

In controlled clinical trials, thrombocytosis has not been reported as an adverse effect in the context of myeloproliferative diseases or graft-versus-host disease. In addition, there are only isolated case reports, and it is not included as an expected adverse effect in commercial pharmaceutical information. This phenomenon is possibly due to multifactorial causes, such as reduction in phagocytic activity, reduction of splenic sequestration, incomplete JAK-2 inhibition, or activation of kinases not yet described with megakaryopoiesis dysregulation [3-7]. To our knowledge, this is the first case of ruxolitinib-induced extreme thrombocytosis in the context of COVID-19 in a patient without hematological disease, and should be considered as an extraordinarily rare side effect, which may increase the risk of fatal thromboembolic events.

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REFERENCES

1. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol 2020;146:137-46, e3.
2. Giudice V, Pagliano P, Vatrella A, et al. Combination of ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-related acute respiratory distress syndrome: a controlled study. Front Pharmacol 2020;11:857.
3. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 2015;372:426-35.
4. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807.
5. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366:787-98.
6. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med 2020;382:1800-10.
7. Polverelli N, Catani L, Vianelli N, Baccarani M, Cavo M, Palandri F. Ruxolitinib- but not fedratinib-induced extreme thrombocytosis: the combination therapy with hydroxyurea and ruxolitinib is effective in reducing platelet count and splenomegaly/constitutional symptoms. Ann Hematol 2015;94:1585-7.

Romiplostim plus danazol as salvage treatment for eltrombopag refractory immune thrombocytopenia: a retrospective pilot study

TO THE EDITOR: The thrombopoietin (TPO) pathway is the primary signaling mechanism that drives platelet production [1]. In healthy individuals, the TPO pathway is activated in response to circulating platelet levels. However, patients with immune thrombocytopenic purpura (ITP) cannot mount an adequate TPO-mediated response to compensate for the immune-mediated platelet destruction, leading to a net decrease in platelet count [2-5]. TPO receptor agonists (TPO-RA) bind and activate the TPO receptor in ITP patients. ITP is effectively treated with TPO-RAs, namely eltrombopag and romiplostim. However, some patients do not benefit from the initially prescribed TPO-RA [6, 7]. Since the pharmacodynamic and pharmacokinetic properties of eltrombopag and romiplostim differ from one another, switching to an alternate TPO-RA is a viable salvage treatment option. Retrospective clinical data reported response rates ranging from 65% to 100% after switching from eltrombopag to romiplostim [8-12]. In this report, we share our experience of switching TPO-RAs in heavily treated ITP patients. The efficacy of romiplostim was maximized by adding danazol.

This was a retrospective pilot study involving adult patients over 18 years old, diagnosed with chronic ITP but failed to respond to corticosteroids, intravenous immunoglobulin, and eltrombopag. The diagnosis and response eval-

uation were performed according to the American Society Hematology guidelines [13]. These patients were treated with romiplostim after failing to respond to eltrombopag. Romiplostim was initiated at 1 μg/kg and escalated weekly until the platelet count reached ≥50×10^9/L. The maximum dose was capped at 10 μg/kg. If the platelet level was not stabilized by the maximum dose of romiplostim, danazol was added at 200 mg once a day per the physician's choice. The dose and duration of danazol treatment were decided by the physician, with the maximum dose capped at 600 mg. Among the 16 patients, eight received danazol. The characteristics of all patients are shown in Table 1. This study was conducted following the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: H-1909-116-1066). The differences between the groups were assessed using the Student's t-test or one-way analysis of variance for continuous variables, and Pearson's chi-square test for categorical variables. Statistical significance was set at $P<0.05$. The data were analyzed using the Statistical Package for the Social Sciences software (SPSS Statistics version 22.0, IBM Corp., Armonk, NY, USA).

All patients underwent bone marrow biopsy to rule out other etiologies before romiplostim administration. The median duration of ITP was seven years (range, 2–28 yr) from the start of romiplostim. There was a median of five prior treatments.

All patients in the group, supplemented by danazol, achieved a complete response (CR) within the median follow-up of 1.4 (range, 0.3–2.9) years. The median time to danazol addition was four weeks, and as shown in Fig. 1 the mean platelet count spiked and stabilized with the addition of danazol. The median time to the best response was 11 weeks. The maximum romiplostim dose was 8 μg/kg per patient, and the median dose was 5 μg/kg. The maximum danazol dose was 600 mg per patient, and the median dose was 300 mg. Once started, the patients continuously received danazol throughout the follow-up period. There were two cases with adverse events. One patient complained of headache, while another complained of tinnitus. For these patients, danazol was discontinued until the symptoms resolved. Upon re-challenge, the patients adequately tolerated the drug, and they continued receiving danazol. Two patients relapsed within three months of romiplostim discontinuation after achieving CR. Romiplostim treatment

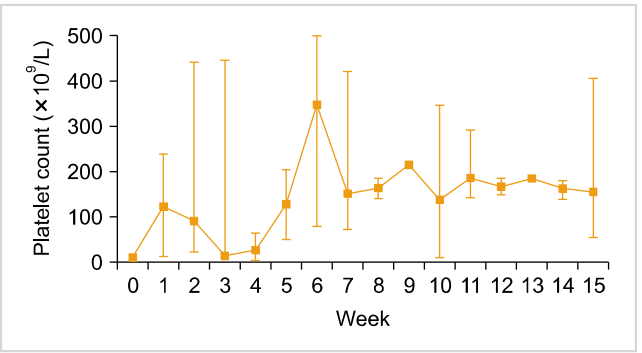

Fig. 1. Mean (±standard error of the mean) platelet count changes during follow-up.

Table 1. Patient characteristics and response.

N, %	Danazol users	Danazol non-users	*P*
N	8	8	NA
Age at ITP diagnosis, years (median, range)	53 (22–75)	61 (37–84)	0.374
Sex, female	7 (87.5)	8 (100)	1.000
Duration of ITP at romiplostim start, years (median, range)	7 (2–17)	7 (4–28)	0.430
N of prior treatments (median, range)	4 (3–7)	5 (3–7)	0.355
Prior treatments			
IVIG/Anti-D	8 (100)	8 (100)	NA
Splenectomy	5 (62.5)	7 (87.5)	0.569
Rituximab	1 (12.5)	4 (50.0)	0.282
Immunosuppressants	2 (25.0)	3 (37.5)	1.000
Corticosteroids	8 (100)	8 (100)	NA
Danazol	5 (62.5)	3 (37.5)	0.619
Eltrombopag	8 (100)	8 (100)	NA
Baseline platelet count, $\times10^9$/L (mean, range)	10.3 (4–21)	7.9 (4–17)	0.362
Best response			
Complete response	8 (100)	6 (75)	0.467[a]
Partial response	0	1 (12.5)	0.302[b]
No response	0	1 (12.5)	
Loss of response	2/8 (25.0)	3/7 (42.9)	
Time to best response, weeks (median, range)	11 (2–22)	13 (3–42)	0.423

[a] *P*-value for complete response rates. [b] *P*-value for partial response or better (i.e. partial response+complete response) rates.
Abbreviations: ITP, idiopathic thrombocytopenic purpura; IVIG, intravenous immunoglobulin; NA, not applicable.

was restarted, and the patients responded well.

Among the 16 patients, eight patients did not receive danazol because they refused, based on their previous experience with the drug and physician's choice [4]. Among these patients, seven achieved a partial response or better (87.5%), while six (75.0%) achieved CR. Due to the study's retrospective nature and the small number of patients, the direct comparison did not show statistically significant differences between the patients who received and did not receive danazol. Considering the 100% CR rate in the danazol recipients, this combination warrants further evaluation.

The promising treatment results of danazol were first documented in 1987 [14]. Since then, it has been used as a second-line treatment for relapsed/refractory ITP. Danazol, a synthetic attenuated androgen, induces platelet elevation by antagonizing estrogen and reducing platelet destruction via immune modulation [3, 13]. Combining TPO-RAs and danazol regulates the pathophysiology of ITP, excessive platelet destruction, and impaired platelet production, ultimately eliciting better responses from ITP patients. In addition, danazol enhances the stability of romiplostim by blocking romiplostim neutralizing antibodies. In this setting, an escalated dose of romiplostim is insufficient to overcome romiplostim resistance. Adding danazol reverses the paradoxical effect of megakaryopoiesis recovery on endogenous TPO levels. However, the exact mechanism of their synergistic effect requires further investigation.

In conclusion, this pilot study showed that 1) TPO-RA switching was a viable salvage therapy option, even in long-standing heavily treated ITP patients; and 2) danazol exhibited a synergistic effect when combined with romiplostim, leading to rapid platelet count stabilization. Based on the results of this study, a prospective phase II study (ClinicalTrials.gov Identifier NCT04289207) will be conducted to corroborate the preliminary findings.

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REFERENCES

1. Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. Int J Hematol 2013;98:10-23.
2. Neunert CE, Cooper N. Evidence-based management of immune thrombocytopenia: ASH guideline update. Hematology Am Soc Hematol Educ Program 2018;2018:568-75.
3. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.
4. Rodeghiero F, Ruggeri M. Treatment of immune thrombocytopenia in adults: the role of thrombopoietin-receptor agonists. Semin Hematol 2015;52:16-24.
5. Cooper N, Bussel J. The pathogenesis of immune thrombocytopaenic purpura. Br J Haematol 2006;133:364-74.
6. Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009; 113:2161-71.
7. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:641-8.
8. González KJ, Zuluaga SO, DaRos CV, Rodríguez PP, Martí AC. Sequential treatment with thrombopoietin-receptor agonists (TPO-RAs) in immune thrombocytopenia (ITP): experience in our center. Ann Hematol 2017;96:507-8.
9. Lakhwani S, Perera M, Fernández-Fuertes F, et al. Thrombopoietin receptor agonist switch in adult primary immune thrombocytopenia patients: a retrospective collaborative survey involving 4 Spanish centres. Eur J Haematol 2017;99:372-7.
10. Kuter DJ, Macahilig C, Grotzinger KM, et al. Treatment patterns and clinical outcomes in patients with chronic immune thrombocytopenia (ITP) switched to eltrombopag or romiplostim. Int J Hematol 2015;101:255-63.
11. Khellaf M, Viallard JF, Hamidou M, et al. A retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia. Haematologica 2013;98:881-7.
12. Tsukamoto S, Nakaseko C, Takeuchi M, et al. Safety and efficacy of romiplostim in patients with eltrombopag-resistant or -intolerant immune thrombocytopenia. Br J Haematol 2013;163:286-9.
13. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019;3:3829-66.
14. Ahn YS, Harrington WJ, Simon SR, Mylvaganam R, Pall LM, So AG. Danazol for the treatment of idiopathic thrombocytopenic purpura. N Engl J Med 1983;308:1396-9.