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CLINICAL TRIALS AND OBSERVATIONS

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Eltrombopag: a springboard to early responses in SAA

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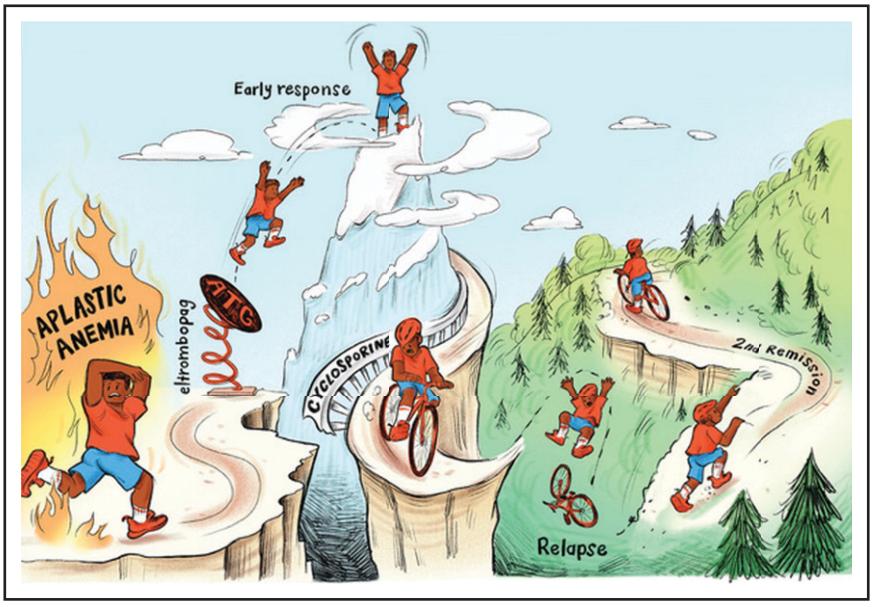
In this issue of *Blood*, Patel et al[1] from the US National Institutes of Health (NIH) report long-term outcomes of the landmark phase 2 trial of eltrombopag combined with immunosuppressive therapy (IST) for upfront treatment of severe aplastic anemia (SAA).

An oral thrombopoietin mimetic, eltrombopag, received initial US Food and Drug Administration (FDA) approval for relapsed or refractory aplastic anemia in 2014, based on responses in ~40% of patients with relapsed/refractory SAA.[2,3] Subsequently, the 2017 phase 2 study found superior hematologic responses in patients with newly diagnosed SAA treated with eltrombopag and IST compared with historical controls who received IST alone,[4] leading to the FDA approval of eltrombopag for newly diagnosed SAA. The 2017 study tested 3 courses of eltrombopag, ranging from 3 to 6 months, administered alongside horse anti-thymocyte globulin and cyclosporine A (CsA). Approximately half of the patients completed eltrombopag and CsA at 6 months, per the study protocol. However, 56% of patients relapsed after treatment discontinuation, leading to a mid-study amendment to include 18 additional months of CsA maintenance. The 2017 study found optimal responses with 6 months of eltrombopag and 2 years of CsA. However, the heterogeneity of treatment schedules in the 2017 study complicated the evaluation of patient responses and response durability. Additionally, limited follow-up left open the question of the long-term safety of eltrombopag in upfront treament of SAA, given the high rates of clonal evolution when used in a relapsed/refractory setting.[2]



Eltrombopag added to immunosuppressive therapy consisting of anti-thymocyte globulin (ATG) and CsA serves as a springboard to more robust early responses; however, challenges remain. Upon cessation of CsA therapy, excellent initial responses are followed by a relapsing/remitting course in a significant fraction of responding patients. Professional illustration by Patrick Lane, ScEYEnce Studios.

In their study, Patel and colleagues analyzed long-term outcomes of 178 patients with SAA who were treated with eltrombopag and IST (92 patients included in the 2017 study and 86 newly enrolled patients); they received eltrombopag for 6 months and CsA for 2 years ("cohort 3 + maintenance"). Results from the extended cohort confirmed that eltrombopag promotes more robust early hematologic responses to IST. At 6 months, 81% of patients treated with IST and eltrombopag achieved hematologic responses compared with 67% of historical controls treated with IST alone. Eltrombopag reduced the fraction of nonresponding patients (29% in historical controls vs 9% on eltrombopag) and increased the number of patients meeting complete response (CR) criteria (17% historical controls vs 39% on eltrombopag). However, the results from the extended cohort showed that the superior hematologic responses were not maintained after eltrombopag was discontinued. Thirty-nine percent of patients treated with 6 months of eltrombopag and CsA maintenance relapsed. At 12 months, the event-free overall response rate (ORR) in the eltrombopag cohort was similar to historical controls (56% vs 57%, respectively). After a median

follow-up of 4 years, ORR was 43%, with 30% of patients remaining in CR.

The timing of relapses relative to eltrombopag and CsA discontinuation offers clues as to the mechanisms involved. The mid-study amendment adding CsA maintenance allows us to compare relapses in 44 patients who discontinued treatment at 6 months with patients continuing CsA maintenance after stopping eltrombopag. The ~17% excess relapse in patients who discontinued CsA at 6 months suggests recrudescence of autoimmune SAA as the relapse mechanism. The same mechanism likely underlies late relapses after the completion of 2-year CsA maintenance. These data are consistent with the dose-dependent effect of CsA on reducing relapse risk in SAA,[5,6] where only 1.5% of the ~30% to 40% of relapses in historical NIH studies occurred within the first year of CsA treatment/taper, with the majority arising later at lower CsA doses or after CsA discontinuation.[6]

In contrast, mechanisms underlying the large number of early relapses after stopping eltrombopag in patients continuing CsA maintenance are less clear but are likely, in large part, nonimmunologic. Eltrombopag enhances hematopoietic recovery by augmenting thrombopoietin signaling, which promotes hematopoietic stem and progenitor cell expansion and megakaryocytic differentiation.[7] Patients with marginal marrow reserves, including older adults and those with incomplete recovery at 6 months, seemed to be most sensitive to stopping eltrombopag. Compared with late relapses, early relapses associated with stopping eltrombopag developed more commonly in patients with partial responses and lower platelet and neutrophil counts. Because relapses were defined broadly as substantial decreases in ≥1 blood count on 2 consecutive samples prompting therapy reinitiation, it is unclear how many eltrombopag-associated relapses represented true SAA recurrences. Of early relapses, 85% involved platelets only, and some of these may have eventually stabilized after stopping eltrombopag.

Whether patients with partial responses at 6 months could benefit from extended eltrombopag therapy remains an open question. Experience in relapsed/refractory SAA suggests that some patients have ongoing improvement with more prolonged treatment.[2] Importantly, although clonal evolution was not increased by adding eltrombopag to IST for newly diagnosed SAA patients, certain populations may be at higher risk, including older adults and (extrapolating from relapsed/refractory patients[2]) those with poor responses who are receiving prolonged therapy. Thus, patients on eltrombopag should be monitored for clonal evolution.

If superior responses on eltrombopag are not sustained, is the addition of eltrombopag to upfront IST clinically meaningful? The results of Patel and colleagues suggest that it is. SAA is a life-threatening disease in which mortality, complications, and quality of life are tied directly to the depth and duration of cytopenias.[8] By promoting early responses, eltrombopag shortens the period of severe cytopenias, reducing the risk of complications and potential need for more toxic therapies. Having only partial responses or relapsing did not worsen overall survival, likely because partial responses were sufficient to prevent life-threatening complications and because most relapses responded to the resumption of therapy.[1,8,9] In contrast, the lack of response to IST predicted higher mortality,[1,8] and eltrombopag effectively reduced the frequency of nonresponders.

Finally, this study serves as a powerful reminder of the chronic nature of SAA: excellent initial responses to IST are followed by a relapsing/remitting course in nearly half of responding patients. Frequent relapses indicate that a short-term treatment strategy aimed mainly at inducing initial responses is not the optimal paradigm for SAA. Instead, SAA should be viewed through the long-term lens of chronic autoimmune disease (see figure) for which maintenance therapy should be routinely included for relapse prevention. Studies are needed to develop early biomarkers of immunologic relapse and safer and more effective relapse-prevention approaches.

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