Thrombopoietin agents and marrow fibrosis: fact or myth

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In their letter entitled, "Overuse of thrombopoietin receptor agonists driven by suboptimal response is associated with myelofibrosis in pediatric immune thrombocytopenia," Ma and colleagues[1] raise an important question that seemed to have been largely resolved by previous studies in children:[2,3] is there a risk of inducing or exacerbating bone marrow myelofibrosis when using thrombopoietin receptor agonists (TPO-RA)? We would like to provide some context for this question.

Early clinical studies, primarily but not solely in adults, had addressed this topic.[4-6] As the authors described, "prolonged TPO-RA exposure has been associated with the development of reticulin fibrosis, a process driven by TPO-induced megakaryocyte hyperplasia and the subsequent release of pro-fibrotic cytokines, primarily transforming growth factor-beta (TGFβ)."

In the first TPO-RA study in immune thrombocytopenia (ITP) using romiplostim, published in October 2006,[4] the initial dose allowed per protocol was, in stepwise fashion, as high as 30 μg/kg administered weekly. One patient with apparent ITP who had been very refractory and had suffered an intracranial hemorrhage in the past was receiving romiplostim at a dose of approximately 10-12 μg/kg/week. His response waned and his weekly dose was increased. At 17–20 μg/kg/week, peripheral smear abnormalities developed and bone marrow evaluation demonstrated findings consistent with myelodysplasia with "myelofibrosis". The drug was withheld and eventually reinstituted at a lower dose. In part as a result of this case, and because few patients required doses above 10 μg/kg/week, Amgen lowered the peak dose allowed per protocol to 15 μg/kg/dose and then to 10 μg/kg/week.[4]

Nonetheless, this case, combined with preclinical toxicology studies, raised concern in the community of hematologists and ITP patients regarding bone marrow fibrosis. As a result, GSK, in its early trials with eltrombopag, arranged for routine bone marrow examinations to be performed.[8] We initiated a similar program at our center of performing bone marrow examinations at certain intervals to explore the risk of reticulin fibrosis.[7] Reassuringly, neither the GSK study nor our study revealed other than very infrequent grade 2 myelofibrosis and no clinical sequelae were identified.[7,8] In some cases, repeat bone marrow examinations not only failed to show progression of the degree of fibrosis, but also documented a regression of fibrosis despite continued treatment. Furthermore, virtually no cases with the highest grade of fibrosis, MF3, were identified.

Recognizing that children represent a distinct population and may also be a risk, the Children's Hospital of Orange County and our center combined to do a small study with romiplostim in which no concerning cases were identified.[2] Subsequently, the Food and Drug Administration asked Amgen, in their multicenter, predominantly European romiplostim study, to explore serial bone marrows in a relatively large number of children.[3] Patients in the study were randomized, after bone marrow sampling prior to initiating romiplostim, to have a repeat bone marrow examination 12 or 24 months later. Again, there were no concerning findings and thus the issue appeared to have been resolved both in adults and in children (Figure 1) although several isolated cases have been reported.

The study by Ma and colleagues now identifies a new version of the bone marrow "myelofibrosis" question. Are very difficult-to-treat patients (children) who had been on high doses of multiple TPO agents and required a maximal or even supramaximal dose of a TPO agent to maintain an adequate platelet count at risk of myelofibrosis? It would appear that the answer is yes. In their analysis, the "offending agent" was virtually always avatrombopag. To the best of our knowledge, specific studies of reticulin fibrosis in adults or children with ITP on avatrombopag have not been performed. It remains unclear whether the finding of reticulin fibrosis in the study by Ma *et al*. is a coincidence because of avatrombopag being the last of multiple TPO agents used in their children or if the reticulin fibrosis is specifically related to avatrombopag, although any of romiplostim, eltrombopag, and avatrombopag could create this effect. Each of these three possibilities has important differences from the other two in their mech-

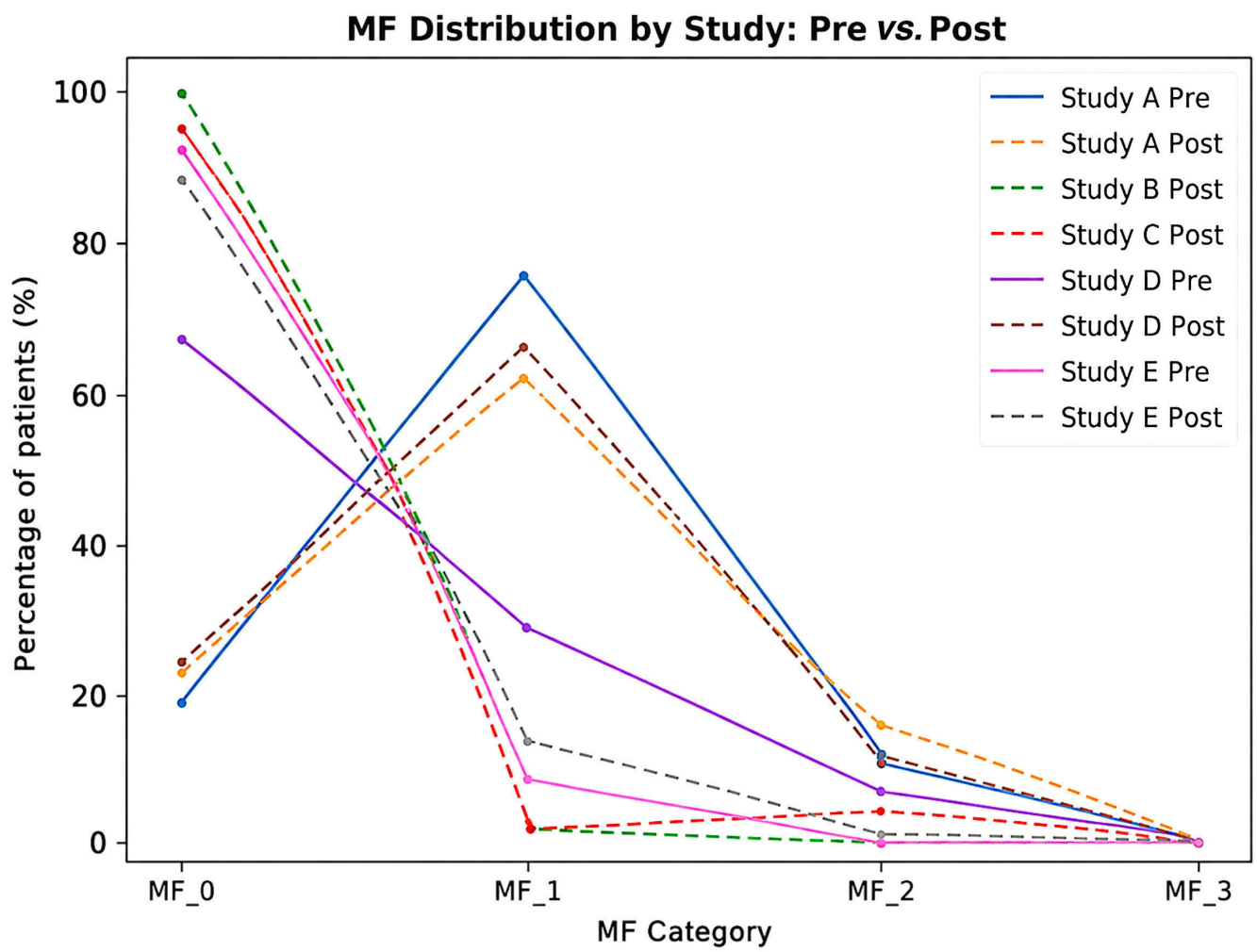


Figure 1. Myelofibrosis grade distribution before and after thrombopoietin receptor agonist therapy across five studies. Percentages of patients in each myelofibrosis (MF) category (MF_0–MF_3) are shown. Pre-treatment data were available for studies A, D, and E only; studies B and C report post-treatment data only. Studies: A (Grainger *et al.*, *Blood Adv.*, 2023); B (Seidel *et al.*, *Br J Haematol.*, 2014); C (Ramaswamy *et al.*, *J Pediatr*, 2014); D (Ghanima *et al.*, *Haematologica*, 2014); E (Brynes *et al.*, *Acta Haematol*, 2017).

anism of action.[9] Therefore, this response could possibly be specific to avatrombopag or only appear that way.

What else do we need to consider here? First, "myelofibrosis" is not true myelofibrosis of the type seen in myeloproliferative disorders. It has usually been reversible when the TPO agent is discontinued. Second, is this intrinsic to the affected patients: do they have an underlying abnormality which renders them relatively insensitive to TPO agents and simultaneously contributes to the marrow fibrosis or could this happen to any child with ITP?

The key message of this manuscript is that if a child, or probably even an adult, with ITP has the dose of a TPO agent increased to the maximum approved level and this does not result in a better effect, then perhaps the safest approach would be to add another agent rather than continuing to increase the dose of the TPO agent. However, individualization and careful monitoring, possibly including bone marrow examination, are required regardless of the choice of management.

Disclosures

JBB is a consultant for Rallybio, Janssen, Union Chimique Belge (UCB), Argenx, Mara Bio, and Recordati. MHH has no conflicts of interest to disclose.

Contributions

JBB conceptualized the editorial, performed the literature review, and drafted the manuscript. MHH contributed to critical revisions, prepared the figure, and assisted with manuscript editing. Both authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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