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Association does not establish causation. Comment on: "Overuse of thrombopoietin receptor agonists driven by suboptimal response is associated with myelofibrosis in pediatric immune thrombocytopenia"

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We read with interest the Letter by Ma et al. on thrombopoietin receptor agonist (TPO-RA) exposure and marrow fibrosis in children with refractory immune thrombocytopenia (ITP),[1] together with the accompanying editorial by Bussel and Hyche.[2] The study addresses a clinically relevant question: whether treatment intensity, rather than duration alone, is associated with fibrosis. Explicit, agent-specific overdose definitions and blinded review by two hematopathologists strengthen exposure and outcome assessment. Follow-up marrow examinations also provide preliminary observations relevant to reversibility. Nevertheless, several limitations constrain causal interpretation.

First, the cohort comprised children biopsied because of suboptimal response or loss of efficacy. Both children with grade ≥2 fibrosis and the comparison group therefore represented a selected, treatment-refractory population. The reported 25.9% frequency describes this biopsy-selected cohort, not the incidence or prevalence among all children receiving TPO-RAs. The authors appropriately acknowledge this limitation.[1] Furthermore, no pre-TPO-RA marrow fibrosis grades were reported. The absence of baseline biopsies limits attribution of fibrosis to treatment, but it does not establish that fibrosis was pre-existing; the timing of its onset relative to TPO-RA exposure simply cannot be determined.

Second, associations between treatment intensification and fibrosis may be susceptible to residual confounding related to treatment indication and disease course.[3] Higher doses and repeated agent switching may reflect disease refractoriness. Refractoriness itself need not be a direct biological cause of marrow fibrosis; rather, factors that accompany it, such as associated clinical characteristics, previous treatments, and longer total treatment duration, may be related to fibrosis and could partly explain the observed associations. The present analysis cannot separate these factors from treatment intensity. The explicit overdose definitions improve reproducibility, but do not establish equivalent biological exposure across agents. Analyses incorporating treatment sequence, cumulative exposure (dose and

duration), and longitudinal measures of disease severity would help distinguish treatment intensity from the clinical circumstances prompting escalation.

Third, drug-specific inference is particularly uncertain. All 14 children with grade ≥2 fibrosis had received avatrombopag, compared with 52.5% of the comparison group; however, avatrombopag was generally used after failure of other agents. This treatment sequence complicates attribution of an independent drug-specific effect, as the authors themselves acknowledge.[1] In addition, the use of hetrombopag and the substantial prevalence of prior recombinant human thrombopoietin exposure reflect the local treatment context, which may limit generalizability to settings with different available agents and treatment sequences.

Fourth, only 14 fibrosis events were available for analysis. Nine variables were assessed in univariable analyses, with variables meeting the prespecified screening threshold considered for multivariable modeling.[1] Given the limited number of events, data-driven model selection raises concerns about the stability of adjusted estimates. The wide confidence interval for overdose (adjusted odds ratio 4.41; 95% confidence interval 1.04–18.58) illustrates this uncertainty.[1,4] Moreover, the time-to-event analysis warrants caution because fibrosis was identified through clinically indicated rather than scheduled biopsies, leaving its onset uncertain. Dose escalation and agent switching are time-varying exposures, but the report does not specify how they were coded or when follow-up began. If children were classified by exposure status reached later in follow-up while follow-up began at TPO-RA initiation, immortal-time bias could arise; whether this applies cannot be determined from the published methods. Clarification of the time origin and exposure coding, together with time-dependent modeling where appropriate, would help assess this potential bias; uncertainty regarding fibrosis onset would nonetheless remain.

Finally, follow-up biopsies were obtained in only eight of the 14 affected children,

and the basis for selecting patients for reassessment was not reported.[1] Regression in all five reassessed patients who discontinued TPO-RAs is reassuring; however, these patients also transitioned to alternative immunomodulatory agents, and incomplete follow-up and concurrent treatment changes limit reliable estimation of reversibility and attribution of regression solely to TPO-RA withdrawal.[1] As noted by Bussel and Hyche, previous studies have documented fibrosis regression despite continued TPO-RA treatment.[2,5] These observations indicate a heterogeneous histological course and caution against assuming that continued exposure invariably produces progressive fibrosis. Histological reticulin fibrosis should also be distinguished from clinically consequential myelofibrosis. Ma et al. reported no statistically significant differences in peripheral blood counts and no teardrop cells between groups.[1] In a mixed-age cohort, higher-grade fibrosis occurred in a subset of TPO-RA-treated patients, although blood counts and lactate dehydrogenase did not differ significantly between fibrosis groups.[5] In a prospective pediatric romiplostim study, no evaluated patient developed modified Bauermeister grade 3 or 4 fibrosis, and increases in reticulin were not associated with worse platelet responses or bleeding.[6] However, marrow evaluation involved a subset of patients, and differences in treatment exposure, biopsy selection, and grading systems limit direct comparison with Ma et al.[1,6]

Overall, Ma et al. provided a valuable, hypothesis-generating safety signal rather than definitive evidence that intensified TPO-RA exposure independently induces marrow fibrosis. Prospective studies incorporating detailed agent-specific exposure histories, longitudinal assessment of disease refractoriness, and, where clinically and ethically justified, baseline and follow-up marrow assessments graded using the European consensus system[7] would help clarify the frequency, reversibility, and clinical significance of these changes.

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