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Response to Comment on: "Overuse of thrombopoietin receptor agonists driven by suboptimal response is associated with myelofibrosis in pediatric immune thrombocytopenia"

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Running head: TPO-RA intensity and marrow fibrosis: reply

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We thank Jaing and Chang for their careful reading of our Letter and for framing the discussion around a distinction we also regard as essential: association versus causation.[1] We agree with their central proposition and with much of their critique. The word “associated” in our title reflects the same caution: we do not claim that intensified thrombopoietin receptor agonist (TPO-RA) exposure independently induces marrow fibrosis.[2] We write to clarify several methodological points that space constraints prevented us from specifying, and to indicate where our data bear on the alternatives they raise.

Jaing and Chang correctly note that the 25.9% frequency describes a biopsy-selected, refractory cohort rather than the incidence among all children receiving TPO-RA, as we ourselves stated. Yet the MF≥2 and MF 0-1 groups were assembled through the same selection mechanism — a marrow examination prompted by suboptimal response or loss of efficacy. Selection operating identically in both groups limits the generalizability of the absolute frequency but does not by itself generate the between-group contrasts we report. The design was deliberate: scheduled biopsies cannot be justified in children for research alone.

The absence of pre-TPO-RA fibrosis grading is our most consequential limitation, and we agree that it precludes determination of onset. Three observations bear on the alternative that fibrosis was pre-existing. First, all patients underwent systematic evaluation, including genetic testing where indicated, to exclude congenital thrombocytopenias, secondary immune thrombocytopenia (ITP) and hematologic malignancy — the principal causes of baseline fibrosis. Second, the exposure gradients are difficult to reconcile with a fixed abnormality: median overdose exposure was 3.0 versus 0.0 months, and among the 20 children ever overdosed the median maximum dose reached 168.5% of the recommended limit for a median of 7.8 months. Third, 15 of the 54 patients — four of whom later developed MF≥2 — had undergone marrow examination before TPO-RA initiation: reticulin fibrosis was graded 0 in 14 and 1 in one. Baseline biopsies were scarce because many children had begun TPO-RA at outside hospitals before referral. The interval from diagnosis to TPO-RA initiation, when all prior treatments were given, did not differ between groups (median 10.3 versus 10.8 months). These observations make a causal interpretation plausible even when it cannot be established.[3]

We accept that confounding by indication cannot be excluded, and we welcome their suggested analyses. Notably, variables reflecting disease burden rather than treatment intensity — prior

treatment lines (median 3.0) and total TPO-RA duration (23.9 versus 16.6 months) — were associated with MF≥2 in univariable analysis but did not survive multivariable modeling, whereas overdose and number of switches did. Had refractoriness per se been the operative mechanism, total duration would be expected to persist. Escalation and switching also followed documented treatment failure, establishing exposure before outcome. Our argument has never been that refractoriness causes fibrosis; it is that within a refractory population the supraphysiological stimulation we add is the modifiable component — hence a prescribing recommendation rather than an etiologic claim.

On model stability, we agree that 14 events impose real constraints. The final model retained two predictors, each with an a priori mechanistic rationale, and we reported fit and collinearity diagnostics. The time-to-event analysis, resting on different assumptions, yielded a concordant estimate (adjusted hazard ratio 4.63; 95% confidence interval [CI]: 1.36-15.76). Bootstrap internal validation (3,000 resamples) gave median odds ratios of 4.70 for overdose and 4.49 for switches, reproducing the original estimates (4.41 and 4.00), with optimism for the area under the curve of 0.022 (optimism-corrected 0.791).[4] The point estimates are therefore stable; the limited number of events is reflected in the width of the confidence intervals rather than in instability of the estimates. We also regret that the time origin and exposure coding were unspecified. Follow-up began at TPO-RA initiation; both exposures were ascertained as cumulative status at biopsy and modeled as fixed covariates, because the exact date of first escalation could not be reconstructed for all children, so we cannot exclude immortal time.[5] Any such bias would operate against our findings: children classified as exposed had by definition to remain event-free until escalation occurred (median overdose exposure 7.8 of a median 18.5 months of treatment), and unexposed person-time credited to them would dilute their event rate and bias the estimate toward the null. Conversely, because fibrosis was detected by clinically indicated biopsy, onset is interval-censored; we therefore reported only MF-free survival comparisons, not incidence rates.

Regarding reversibility, we acknowledge that follow-up biopsies were obtained in only eight of 14 children. Repeat examinations were performed as part of routine re-evaluation a median of 6 months after a change in treatment strategy; we did not prespecify selection criteria, and clinical considerations and parental preference determined whether the procedure was repeated. The

internal contrast remains informative: among contemporaneously reassessed children, all five who discontinued TPO-RA showed regression, whereas all three who continued maintained MF≥2. We agree that the concurrent transition to alternative immunomodulatory agents may have contributed to regression, and regard this as support for — rather than a competing explanation of — the management recommendation we made. We also agree that reticulin fibrosis should be distinguished from clinically consequential myelofibrosis, and note that our specimens were graded using the European consensus system,[6] the standard Jaing and Chang themselves advocate. Comparison with earlier series is limited by differences in age composition, agents, biopsy selection and grading systems — as those authors recognize.[7,8]

In closing, we share the view that our findings constitute a hypothesis-generating safety signal rather than definitive evidence. The practical question is what should follow when randomized trials of prolonged supratherapeutic dosing are neither feasible nor ethical. Our recommendation does not require the causal claim against which Jaing and Chang caution: we do not propose withholding TPO-RA from responders. We propose not exceeding approved weight-based doses, not rotating repeatedly among agents that have already failed, and preferring timely transition to alternative immunomodulatory therapy over prolonged off-label intensification. Prospective registries with baseline and scheduled follow-up marrow assessment graded by European consensus criteria are needed, and we welcome collaboration toward that end.

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