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Etanercept as Adjunctive Primary Therapy in Kawasaki Disease

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Abbreviations:

Kawasaki disease (KD)

Intravenous immunoglobulin (IVIG)

Tumor necrosis factor (TNF)

Coronary artery (CA)

Primary treatment of Kawasaki disease (KD) with a single infusion of intravenous immunoglobulin (IVIG) reduces the risk of coronary artery (CA) dilatation and aneurysms, but IVIG resistance occurs in 10-20%.[1] Intensification of primary therapy with adjunct anti-inflammatory therapies to reduce IVIG resistance is therefore of considerable interest, either universally or in selected sub-groups. Among the armamentarium of anti-inflammatory agents that could be added to IVIG therapy, blockade of inflammatory cytokines (such as tumor necrosis factor, TNF), which are markedly increased in KD, is logical. However, a randomised trial of infliximab, a chimeric monoclonal anti-TNF antibody, in unselected KD patients did not reduce IVIG resistance, defined as recurrent or persistent fever at least 36 hours after completion of an IVIG infusion.[2] Infliximab was associated with fewer days of fever and more rapid improvement in inflammatory markers, but only a borderline smaller dimension of the left anterior descending CA at two weeks, of uncertain clinical significance.[2]

In this edition of *Pediatrics*, Michael Portman and collaborators report results of a North American multicenter randomized controlled trial of etanercept, a soluble TNF-receptor fusion protein, as adjunctive primary treatment in unselected KD patients.[3] Unlike infliximab, etanercept binds only soluble and not tissue-associated TNF,[4] but may have theoretical

therapeutic advantages, such as lack of development of anti-drug antibodies; whether these differences are important in acute (as opposed to chronic) inflammation is unknown. As in previous studies of infliximab,[2] the primary end point was IVIG resistance. To assess the secondary outcome of CA dilatation, investigators pre-specified within-individual changes in CA z-scores (adjusted for body surface area, BSA) based on serial measurements of CA diameters at presentation, week 2 and week 5-6. CA dilatation was defined as a z-score of >2.5, as per the AHA Guidelines.[1] Two statistical approaches were used; general estimating equations (GEE) to assess intra-individual change in CA dilatation, and an absolute change in CA diameter of > 20%.

Similar to the findings in the primary infliximab trial,[2] etanercept did not reduce IVIG resistance. Unfortunately (at least statistically), the rate of IVIG resistance was lower than in the pilot on which sample size was based and the study was underpowered for the primary outcome. There was also little evidence of overall differences in CA dilatation between the etanercept and placebo groups, although in certain subgroups (> 1 year of age, African American ethnicity), there was evidence of benefit on progression of CA dilatation in the etanercept group that warrants replication in an independent cohort.

The findings of this carefully performed study highlight generic issues that dog trials of adjunctive therapy in KD, including the relatively low frequency of CA aneurysms -

the most clinically important outcome. IVIG is an effective therapy and it would be unethical to withhold IVIG in the comparator group, limiting the power of studies of universal treatment to detect a significant difference in KD outcomes. Randomized trials of primary therapy for KD using anti-inflammatory therapies adjunctive to IVIG would be more efficient if conducted in a high-risk population. To that end, better risk scores for non-Japanese patients are sorely needed.[5] The study also suggests possible differences in response to etanercept by age and race, which necessitate considerably larger sample sizes than studied here. In particular, African American children might benefit most from etanercept in reducing IVIG resistance rate, but their sample size was small (n=21). International collaborative trials across multiple ethnic groups are warranted, but with an increasing number of adjunctive treatments suggested, including other biologics, it may be difficult to reach consensus on prioritizing interventions.

There are some additional considerations. Center variation in KD management may be considerable and may contribute both to residual confounding and reduced power to detect differences in treatment groups, but the authors did not stratify randomization within center. Although IVIG resistance was lower in the subgroup of children who were > 1 year of age, the rate of resistance was somewhat higher with etanercept treatment in infants < 1 year (27% vs. 17%). Ultimately, coronary artery aneurysms are the most important outcome of KD.

The authors used GEE methodology to look at changes in z-scores over time only within each treatment group, but not between groups. As z-scores are based on BSA, and body weight may vary considerably during acute KD treatment, power to detect a difference in z scores might have been enhanced by applying baseline BSA to all z-scores, or simply analyzing absolute within-patient changes in CA diameter over the short time frame of the study over which somatic growth is limited.

Overall, the findings suggest that etanercept may have modest effect in reducing IVIG resistance and CA dilatation in certain subgroups. In the broader context, non-specific (e.g. corticosteroids) and targeted (e.g. anti-cytokine biologics) anti-inflammatory adjunctive therapies are likely to benefit selected subgroups in KD. The key issue of "which therapies for which subgroups" could be resolved by much larger, international collaborative studies, as successfully employed in pediatric HIV and oncology but have yet to gain traction in the KD community. An alternative approach requiring a smaller sample size would be to conduct randomized trials of primary adjunctive therapy in children at high risk for CA aneurysms. Finally, basic and translational research is needed to optimise our understanding of the immunologic underpinnings of KD to find specific targeted therapies for this enigmatic and potentially life-threatening disease.

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