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Seeking similarities rather than differences with adults to aid in therapeutic advancement for children

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Commentary on Singh et al. *“Response similarity assessment between polyarticular juvenile idiopathic arthritis and adult rheumatoid arthritis for biologics” PMID 33626206*

Drug development for children continues to lag behind that in adults, particularly in neonatal and rare disease populations.⁽¹⁾ Historical reasons include economic incentives, regulatory barriers, scarcity of widespread expertise in the conduct of pediatric clinical trials, a paucity of known biomarkers in children, a conservative ethical framework, and lack of consensus for a widely accepted development path. Ontogeny of drug biotransformation and response is also a key factor unique to children that makes drug development hard. Physiologic changes spanning infancy through adolescence can differentially impact drug pharmacokinetics (PK). Age and disease-specific factors impacting pharmacodynamics (PD) are equally important but often elusive, especially in rare rheumatic conditions.

Despite these inherent challenges, since the approval of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), there has been an increase in both the number of clinical trials conducted in pediatrics and number of regulatory approvals for indications in children.⁽²⁾ The importance of a favorable regulatory framework is indicated by the larger number of pediatric supplemental indication approvals in the US and Europe compared to Japan, which lacks comprehensive legislation to mandate or incentivize drug development in children.⁽³⁾ While the drivers ultimately come from specific regulatory and legislative directives, the framework for such has been fostered by thought leaders within the FDA, academics, and industry, often brought together in collaboratives such as IQ Consortium, Critical Path, and Institute for Advanced Clinical Trials for Children (I-ACT).

Given the barriers to the conduction of pediatric clinical trials, use of extant adult data is relevant to drug development in children as a strategy to demonstrate a drug is “reasonably safe and effective” in children. A key tool has been a framework and decision tree outlined by the FDA in the 2014 guidance on clinical pharmacology considerations for pediatric studies.⁽⁴⁾ Unless there is a reasonable assumption of similarity in 1) disease progression or 2) response to intervention in both adults and children, there is no role for extrapolation. In contrast, if both are present, there is the potential to bring in adult data to inform drug development in children. Furthermore, if there is both a reasonable assumption of 1) similar exposure-response and 2) a measurable drug concentration predictive of response, the drug qualifies for “full extrapolation”. If one or both cannot be met, the drug pathway can use “partial extrapolation”. The practical difference is that full extrapolation allows an adequate PK study in children to match a dose to an exposure associated with efficacy in adults. Partial extrapolation extends requirements for adequate dose ranging trial(s) that demonstrate the ability to reach a target PD effect. The EMA has endorsed a similar philosophy, with a focus on the uncertainty that surrounds the evidentiary base to make assessments of similarity in disease progression and exposure response.⁽⁵⁾ Simply put, extrapolation can serve as wind to the back of drug development in children. The key consideration is relevancy of the specific adult data to the specific pediatric indication.

It is against this background that the investigation outlined by Singh and colleagues (PMID 33626206) is welcomed to advance therapeutics in polyarticular juvenile idiopathic arthritis (pJIA). Juvenile idiopathic arthritis (JIA) in its heterogeneous entirety is the most common chronic rheumatic disease of childhood, however, the absolute number of patients with the polyarticular subset of JIA (arthritis affecting 5 or more joints) is smaller, with incidence of 0.3 to 6.5/100,000.⁽⁶⁾ Robust efficacy clinical trials in pJIA are difficult to conduct due to enrollment barriers secondary to both the rarity of the patient population and the scarcity of subspecialty providers. In addition, the incorporation of a placebo arm and the latency for study completion of large prospective clinical trials results in an unacceptable delay to access important treatments; and as more therapeutic options exist, patients and providers have greater access to alternative treatment options, further narrowing the eligible population for clinical trials.⁽⁷⁾ Therefore, extrapolation of data from adults to children is an exciting approach to enhance access to effective drugs; however, the gap in knowledge regarding similarities in exposure and response in pJIA remained a significant obstacle to qualify for “full extrapolation”. Singh sought to examine the exposure-response relationship for biologic agents in adult RA and pJIA by extracting PK and clinical data from 9 phase II-III clinical trials for 4 approved RA

biological products and 4 randomized pivotal JIA trials (3 of which were double blind withdrawal studies). The analysis examined 4 different biologic products (infliximab, adalimumab, golimumab, and tocilizumab) with two different biologic targets well characterized in RA and JIA (tumor necrosis factor-alpha and interleukin-6). Two products (infliximab and golimumab) approved in rheumatoid arthritis (RA) failed to meet the primary endpoint in pJIA.

Drug exposures for all agents in pediatric patients were similar or higher compared to adults, with the exception of children ≤ 35 kg receiving 3 mg/kg dosing of infliximab. This is interesting and potentially important in light of the fact that the placebo-controlled RCT of infliximab in pJIA did not meet its primary endpoint leading to a lack of labeling for pJIA despite its notable effectiveness and use off-label in children.⁽⁸⁾ Age or development-related differences in drug disposition may play a role with infliximab, supported by reports of an inverse relationship between age and infliximab clearance in JIA,⁽⁹⁾ as well as the need for higher doses to reach adequate drug trough concentrations in younger patients with inflammatory bowel disease.⁽¹⁰⁾

Exposure–response was then explored utilizing the subcomponents of the composite American College of Rheumatology core set criteria (ACR20 in RA and pACR30 in JIA), two widely accepted validated outcome measures. Although they differ somewhat, several core components of the composite measures overlap. Of the products investigated, only the failed pJIA infliximab trial could be compared directly as it was similar in design to the adult studies, and response for many measures when overlaid with adults was similar in children, even when data were stratified by weight and corrected for placebo response. The one subcomponent that was notably different was the physician assessment of overall disease activity, which interestingly had a less robust change from baseline compared to adults, and begs the question: for a subjective measure such as this, are there inherent differences in how providers rate disease activity between adults and children? For the 3 other products, pediatric-specific trials were conducted through a double blind withdrawal design, thus only data from the open label phase of the trials were compared to adult data. Again, pediatric patients had similar or better percentage improvement for the core clinical response subcomponents at similar drug exposures to adults. A major criticism of the double blind withdrawal design is the potential to overestimate the treatment effect towards responders by excluding non-responders prior to randomization and in drugs with a long half-life (such as golimumab) where there may be a carryover effect from the treatment period into the double blind withdrawal period.⁽⁷⁾ Supportive of such, golimumab did not achieve the primary endpoint in the pivotal trial in pJIA trial,⁽¹¹⁾ where a prolonged treatment effect into the double blind withdrawal period may have contributed to

similar flare rates and clinical remission rates between active drug and placebo groups. Despite this, its recent approval in pJIA was based on the open label, single arm GO-VIVA phase 3 clinical trial in children with pJIA and juvenile psoriatic arthritis enrolled across 9 countries and similarities in exposure and response compared to 2 pivotal phase 3 trials in adults. In this line of thought, recognizing the challenges in conducting and executing traditional RCTs in children with rare disease, the authors take the approach of gathering a broad base of high quality exposure and response data across different drugs and individual drug classes, and they are the first to compare response and exposure systematically with similar response criteria between RA and pJIA. This bridges an important gap in knowledge that has limited prior qualifications for full extrapolation. Their approach of quantitative methods has been advocated to test the strength of underlying assumptions of extrapolation.⁽¹²⁾

Despite this great step forward, challenges remain. Response rates even with the current options leave many patients with suboptimal control of their symptoms and at risk for long term morbidity and disability. Median AUC_{ss} values will not capture the patients who, for yet unrecognized reasons, require personalized drug dosing. We cannot yet predict at onset which individual patient requires which target-specific therapy, and new disease targets continue to be discovered as the pathophysiology of these conditions are revealed. Additionally, although the assumption of similarity of treatment response to drug exposure generally held, RA and pJIA are not the same disease. Besides the unique contribution of ontogeny upon drug biotransformation in children, there are also differences in inflammatory patterns, biomarker expression,⁽¹³⁾ and natural history.⁽¹⁴⁾ Polyarticular JIA is but one subtype that resides under the clinically heterogeneous umbrella diagnosis JIA, and it is recently recognized that the current clinical and age-driven disease classification for JIA may need to be reconsidered and ultimately driven by a more biologic basis.⁽¹⁵⁻¹⁷⁾ It is the genetic and biologic similarity between pJIA and RA that further justifies extrapolation as a mechanism for drug approval in children. It is possible that in the future with ongoing identification of meaningful biomarkers of drug response, endotypic classification according to the underlying biologic mechanism and response to treatment could drive more precise and efficient management of children and adults alike.⁽¹⁸⁾ However, in our current state, the approach that Singh and colleagues took to capitalize on PK-PD data from pivotal clinical trials to support exposure-response similarities between RA and pJIA is the type of innovative approach we need to move the field forward and promote safe and effective therapeutics to children who need them.

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