Published in final edited form as:

Arthritis Rheumatol. 2018 August ; 70(8): 1172–1174. doi:10.1002/art.40501.

Toward personalized treatment for systemic juvenile idiopathic arthritis

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The past 15 years have witnessed substantial gains in the understanding of systemic juvenile idiopathic arthritis (systemic JIA), also known as Still's disease. Although classified under the JIA umbrella, this rare chronic inflammatory disorder presents with fever and rash in addition to arthritis and is thus phenotypically distinct from other forms of JIA. In a landmark paper in 2005, Pascual and colleagues demonstrated a major role of interleukin (IL)-1 in systemic JIA (1). This observation spurred great interest in therapeutic IL-1 blockade, initially in systemic JIA refractory to other agents and later as first-line treatment (2–4). The pro-inflammatory cytokine IL-6 has proven to be important as well, with clinical response to IL-6 blockade at least as robust as to IL-1 blockade in established systemic JIA (5) (6).

Although therapeutic options are now remarkably better than they were, we still do not know how to decide *which* systemic JIA patient to start on *which* treatment and *when*. This challenge reflects the heterogeneity of systemic JIA. Based on data from existing cohorts, approximately half of patients follow a persistent course, characterized by chronic arthritis and sometimes intractable systemic inflammation. In the remainder, the disease ultimately enters long-term remission, sometimes after only a year or two. Until now, there is no way to tell in advance which course a child will follow. When a biologic is contemplated, it can be difficult to choose between IL-1 and IL-6 blockade. Clinical experience shows that some patients respond to one but not the other, but who are these children? For example, approximately 30% exhibit an incomplete response to IL-1 blockade, even early in disease (3). Despite biologic therapies, there is even in 2018 a substantial subset of systemic JIA patients who remain uncontrolled in the face of all we have to offer. Further, 10–30% of systemic JIA patients develop the explosive “cytokine storm” termed macrophage activation syndrome, and some will develop life-threatening interstitial lung disease and pulmonary hypertension. As a result, management of systemic JIA leaves much to be desired, and identification of predictive biomarkers for therapy response remains a major research priority.

In this issue of *Arthritis & Rheumatology*, Arthur and colleagues present the latest study from the INCHARGE systemic JIA consortium, led by the National Institute of Health's Dr. Michael Ombrello (7). Employing a cohort of 770 systemic JIA patients and 6947 healthy controls patients from the United States, the United Kingdom, Germany, Turkey, Italy, Brazil, Argentina, Canada and Spain, they had previously used genome-wide association study (GWAS) methodology to identify the major histocompatibility complex II region on chromosome 6 as a key genetic risk locus for systemic JIA, and showed that systemic JIA is genetically distinct from more common forms of JIA (8) (9). Here they extended these studies to test 26 single nucleotide polymorphisms (SNPs) – common DNA variants within the population that signpost haplotypes to identify genetic regions associated with disease risk – in 11 loci that had been previously implicated in systemic JIA. These loci included plausible contributors to disease biology, including *IL1A/B*, *IL1R2*, *IL10/20*, *IL6*, and *MVK*. However, like many genetic associations derived from small studies, none of these 26 SNPs replicated in the larger cohort. Extending this analysis to other SNPs within these 11 regions, only one locus emerged as significantly associated with systemic JIA risk – *IL1RN*, encoding the IL-1 receptor antagonist (IL-1ra), an endogenous IL-1 blocking protein familiar to clinicians in its recombinant form as anakinra. While it remains possible that the previously-reported associations could still hold true in specific populations, these results are important because they confirm one genetic risk locus for systemic JIA while steering investigators away from others that could potentially mislead.

Delving deeper into *IL1RN*, Arthur and colleagues employed publically-available data to explore the functional significance of the associated variants. The SNPs most closely associated with risk were not coding variants but rather resided in the *IL1RN* promotor region, raising the possibility that the associated haplotype modulates gene expression. Indeed, these SNPs had previously been identified as *IL1RN* expression quantitative trait loci (eQTLs) – that is, they track with *IL1RN* expression, in both whole blood and in cultured cells. Published data had correlated protective SNPs with higher IL-1ra protein levels in blood. Finally, RNA sequencing data from 373 lymphoblastic cell lines derived from genotyped donors in the 1000 Genomes Project showed that SNPs associated with lower systemic JIA risk correlated with higher *IL1RN* expression, while higher-risk SNPs correlated with lower *IL1RN* expression. Together, these data suggest (although they do not formally prove) that genetic variants in the promotor region of *IL1RN* modulate risk for systemic JIA through their effect on IL-1ra levels.

What are the clinical implications of these findings? As a next step, Arthur and colleagues hypothesized that patients with systemic JIA who already had genetically high levels of IL-1ra might not respond as well to anakinra (i.e. even more IL-1ra) as those whose levels were lower. In fact, this is what they observed. Analyzing 38 patients from their cohort who had received anakinra and for whom response data were available, they found that the 9 anakinra non-responders were more likely to be homozygous for high-expressing *IL1RN* alleles than the 29 responders. By contrast, no such associations were observed among 14 patients with known response data after treatment with the IL-6 receptor antagonist tocilizumab. Some tocilizumab responders had previously received anakinra, suggesting that the correlation between high endogenous IL-1ra and anakinra failure was specific to this therapeutic mechanism, not a marker of refractory disease in general. Thus, the data from

Arthur and colleagues not only define a new gene implicated in systemic JIA but also suggest a genetic marker that may allow pediatric rheumatologists to decide which biologic to use in the clinic.

Strengths of this study include the number of systemic JIA patients, yielding statistical power sufficient to provide some of the first really reliable genetic risk data, and also its potential clinical and translational relevance. However, as the authors emphasize, the genetic predictor of therapeutic response still has to be interpreted with caution. Clinical data were extracted *post hoc* from medical records, and the number of patients with treatment response data was low: only 38 patients on anakinra and only 14 patients on tocilizumab, all from the US. Treatment was not standardized, rendering it difficult to exclude confounders such as dosing, timing (new-onset vs. established disease), and concomitant therapies. The authors sought to simplify the interpretation of chart review data by classifying patients into “non-responders” and “any responders.” This certainly makes sense, but it constrains the resolution of the analysis. As a result, prospective validation will be essential before these genetic variants can be employed for clinical decision-making. Importantly, although widely employed, anakinra is not yet FDA approved for systemic JIA in the United States. The anti-IL-1 β monoclonal antibody canakinumab is approved for this disease, and while one might expect *IL1RN* variants to predict therapeutic response, this possibility was not testable in the present study and thus requires confirmation.

The findings raise additional questions as well. Which genetic variants in the *IL1RN* promotor are responsible for the change in gene expression, and how is this change mediated? Regulatory variants commonly alter gene expression by modulating the binding of transcription factors. Identification of these transcription factors will link the regulation of *IL1RN* to cellular pathways and thereby suggest new targets for intervention (10). How is systemic JIA that evolves in high-IL-1ra children different demographically, clinically, and pathophysiologically from sJIA that does not? Finally, what are the implications of *IL1RN* variants for other conditions in which IL-1 has been implicated, including rheumatoid arthritis, Kawasaki disease, and atherosclerotic cardiovascular disease?

Currently, there are no validated international guidelines for the treatment of systemic JIA. Through the first decade of this century, corticosteroids were the mainstay of treatment worldwide, often in high doses and for prolonged periods, with attendant short- and long-term side effects. Increasingly, reliance on corticosteroids is being minimized in favor of early IL-1 or IL-6 blockade. Given the rarity of systemic JIA and the comparable efficacy of canakinumab and tocilizumab in registration studies, adequately-powered randomized controlled trials comparing IL-1 and IL-6 blockade are likely unrealistic. One potential solution to this problem is the use of observational methodology, such as the FROST study (FiRst-line Options for Systemic JIA Treatment), currently underway within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) network to compare conventional and biologic therapies in new-onset systemic JIA (11). Additional mechanistic understanding is also critical to improving disease outcome, including better definition of biological heterogeneity within systemic JIA, insight into pathways mediating systemic and articular inflammation during different phases of the disease, and the discovery and validation of biomarkers predicting disease course and therapeutic response (12). A better

grasp of disease pathophysiology, building upon the work of Ombrello and co-investigators, promises to open up a new era in pediatric rheumatology: the transition from one-size-fits-all treatment to tailored therapy. When replicated in a separate cohort, preferably in the context of prospective standardised treatment, the present study will be recognized as the first major step toward personalized medicine in systemic JIA.

Acknowledgments

Both authors contributed to this commentary and take full responsibility for its contents.

SJV was supported by the Dutch Arthritis Association (grant LLP10) and ZonMW (Dutch Scientific Organisation, rational pharmacotherapy program). PAN was supported by National Institutes of Health grants R01AR065538 and P30AR070253, by a Disease Targeted Research Award from the Rheumatology Research Foundation, and by the Fundación Bechara.

Disclosures:

SJV is the recipient of an investigator-initiated research grant from a public-private program on rational pharmacotherapy (sponsored by the Dutch Scientific Organisation, Zon MW, co-funded by SOBI) and consulting fees from Novartis.

PAN is the recipient of investigator-initiated research grants from AbbVie, Novartis and Sobi; consulting fees from Casebia, Novartis, Pfizer, SOBI, and UCB; salary support from the Childhood Arthritis and Rheumatology Research Alliance; and royalties from UpToDate and the American Academy of Pediatrics.

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