Are we closer to personalized therapy in juvenile idiopathic arthritis?

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disorder in children. However, actually this term encompasses a heterogeneous group of disorders. Their classification is based on clinical and laboratory features occurring in the 6 months after the disease onset. Most importantly, different subtypes of JIA can still be associated with permanent disability and significant morbidity.

Over the last decades a dramatic improvement in treatment of JIA has been noted. Introduction of methotrexate (MTX) in the late 1980s was the first milestone, described as the first revolution in this disease [1]. This caused transformation of JIA from an untreatable disease into a manageable condition. Unfortunately, although the therapeutic benefits of MTX in JIA are well established, only 30–50% of children have an adequately effective response to this treatment, and several adverse effects are noted in many patients. In 2011 Hinks et al. [2] reported a study in JIA patients which demonstrated that tagging single nucleotide polymorphisms (SNPs) across genes involved in the MTX metabolic pathway could reveal MTX efficacy. Three years later, the first large genome-wide pharmacogenetic study in JIA patients ($N = 759$) treated with MTX reported novel pathways in the MTX-induced response and identified three genes of particular interest (*CFTR*, *TGIF1* and *ZMIZ1*) [3].

Ten years after MTX implementation, the introduction of biologically targeted agents led to a second leap forward in the treatment of JIA. It is one of the few real successes of translational medicine in the past decades. Although further experiences have proven that sometimes drugs inhibiting specific inflammatory pathways failed in JIA, they were found to be efficient in other chronic inflammatory diseases [1].

Over the past decade, the increased therapeutic possibilities resulting in improvement of JIA outcome have changed the way of its definition and classification. The goal for future treatment will be not only to suppress clinical symptoms, as currently, but to achieve an immunologically inactive status. Better understanding of JIA pathogenesis, mechanisms of targeted drug action and identifying biomarkers will be helpful in predicting prognosis, response to treatment and risk of side effects in individual JIA patients. This is the way to achieve personalized strategies for tapering or intensifying therapy in JIA [1, 4–9].

Biomarkers in juvenile idiopathic arthritis

To date, a few biomarkers have been used in routine practice in JIA, including rheumatoid factor (RF), antinuclear antibodies (ANA) and HLA-B27 antigen. However, a number of new biomarker candidates are under development with the aim of predicting disease severity and activity, response to therapy, and risk of complications, and defining JIA subtypes.

In children with oligoarthritis JIA, significant differences in cell frequencies (particularly CD4+ and CD8+), levels of inflammatory mediators (CCL5, also known as RANTES) and gene expression profiles in the inflamed joints between persistent and extended subtypes of the disease have been reported [9]. In the systemic type of JIA (s-JIA), the levels of several proinflammatory S100 proteins, namely S100-A8, S100-A9 and S100-A12 (also known as myeloid-related proteins, MRP-8, MRP-14 and MRP-6, respectively), proved to be sensitive markers of JIA activity. They correlate closely with other activity indices, such as the physician's global assessment of disease activity (PGA), the Childhood Health Assessment Questionnaire (CHAQ), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [8, 10]. The levels of both plasma and synovial fluid IL-18 were significantly higher in s-JIA in remission than in active disease. Moreover, their concentrations correlated positively with CRP levels and number of active joints. Interestingly, a 17-peptide panel of urinary biomarkers could dis-

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tinguish between individuals with the active, quiescent or remission form of s-JIA [8]. To avoid exposure to the potential toxicity of ineffective treatment and facilitate implementation of appropriate therapy at an early stage of JIA, predictive biomarkers are needed. Interleukin 18 seems to be a promising biomarker also for response to therapy in s-JIA. The concentration of this cytokine (as well as S100-A12, S100-8 and S100-A9) is normalized after 3 months of treatment with the IL-1 antagonist anakinra, as a first line agent in most responding patients [1, 5, 8, 10].

In the CHARM (Childhood Arthritis Response to Medication) study the concentrations of S100 proteins (MRP-8-MRP-14 complex) at baseline were significantly higher in patients who achieved an ACR pediatric 50% or greater response after 6 months of MTX treatment than in children who failed to respond [8].

A substantial issue is confirming remission and predicting relapse. A randomized clinical trial conducted in 364 JIA patients showed that 12-month withdrawal of MTX did not reduce the relapse rate compared to 6-month MTX withdrawal in children with clinical remission [1]. Moreover, elevated concentrations of S100 proteins (MRP-8-MRP-14 complex) associated with an increased risk of flare after MTX discontinuation [1]. Additionally, high levels of MRP-6 and MRP-8-MRP-14 complex were detected in patients who experienced relapse within 6 months of MTX treatment discontinuation, whereas the CRP levels measured by high-sensitivity assay were similar in relapsed patients and those with remission [1]. Therefore, in routine clinical practice, MRP-6 and MRP-8-MRP-14 complex levels can be used as a predictor of relapse after stopping MTX treatment.

A life-threatening complication of active s-JIA is macrophage activation syndrome (MAS), characterized by proliferation and activation of macrophages and T cells, occurring clinically in 10% of patients. However, the subclinical form of MAS is prevalent even in 30–40% of s-JIA patients. Prompt diagnosis and implementation of proper treatment is important, but usually very challenging.

Several diagnostic and predictive biomarkers of MAS have already been described. In subclinical MAS, serum soluble IL-2 receptor α (sIL-2Ra, also known as CD25) and soluble CD163 (sCD163, also known as scavenger receptor cysteine-rich type 1 protein M130) are important. During acute MAS, serum follistatin-related protein 1, a glycoprotein overexpressed in certain inflammatory diseases, was significantly elevated and normalized after efficient treatment [8]. The ferritin/ESR ratio was found to be a better marker of differentiation of overt MAS and new onset of s-JIA than ferritin alone [8]. Additionally, on the basis of serum cytokine profile, as either IL-6 dominant (prone to arthritis) or IL-18 (prone to

MAS), two distinct subsets of patients with s-JIA could be defined [1, 8].

In conclusion, a combination of sensitive biomarkers in JIA could allow targeted and personalized treatment and improve outcomes in the near future.

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The author declares no conflict of interest.

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