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Update on research and clinical translation on specific clinical areas: From bench to bedside: How insight in immune pathogenesis can lead to precision medicine of severe juvenile idiopathic arthritis

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A B S T R A C T

Despite the enormous progress in the treatment of juvenile idiopathic arthritis (JIA), innovations based on true bench-to-bedside research, performed in JIA patients, are still scarce. This chapter describes novel developments in which clinical innovations go hand in hand with basic discoveries. For the purpose of this review, we will mainly focus on developments in severe forms of JIA, most notably systemic JIA and polyarticular JIA. However, also in less severe forms of JIA, such as oligoarticular JIA, better insight will help to improve diagnosis and treatment. Facilitating the transition from bench to bedside will prove crucial for addressing the major challenges in JIA management.

If successful, it will set new standards for a safe, targeted and personalized therapeutic approach for children with JIA.

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Introduction

Over the past decades, the treatment of juvenile idiopathic arthritis (JIA) has improved tremendously. The first and often overlooked 'game changer' was the introduction of methotrexate (MTX) in the late 1980s. MTX transformed JIA from a crippling and often almost untreatable disease into a manageable disease. In fact, it offered the first real disease-modifying treatment for JIA [1]. Until the introduction of MTX, other disease-modifying anti-rheumatic drugs (DMARD) such as gold complexes and penicillamine were commonly used [2,3]. Not until years after their introduction, they were proved to be not better than placebo, however, with far more, and sometimes serious, side effects [4].

It is important to realize that MTX thus represented the first major revolution in JIA and still forms a crucial part of its management. Interestingly, the development of MTX as therapy in rheumatoid arthritis (RA) was not the consequence of a well-thought development from bench to bedside. Initially, it was conceived that MTX would inhibit purine and pyrimidine synthesis and consequently reduce T cell proliferation in the synovial tissue. However, the mechanisms of action of MTX in arthritis does not seem to be the consequence of direct suppression of cell proliferation, and to date, still many questions linger around the exact mechanisms of MTX in suppressing arthritis [5].

About 10 years later, the introduction of biologicals led to a second leap forward in the treatment of juvenile arthritis. The importance of the emergence of the therapeutic use of biologicals even goes beyond its proven significance for the treatment of arthritis. It is one of the few real successes of translational medicine in the past decades. While the development of many immune-targeted therapies have failed somewhere along the translational itinerary, the use of biologicals to block specific inflammatory pathways proves to be efficacious in many other chronic inflammatory diseases. This is a bit surprising taking into consideration that the first biological therapy directed at the tumour necrosis factor alpha (TNF-α) pathway initially was developed for intervention in sepsis [6], without success.

Here, we will describe recent advances for the management of JIA and future steps that may be expected in the coming years. We will focus on developments that arise from true translational research. In this, we will mostly restrict this discussion to severe forms of JIA.

What makes severe JIA severe?

As mentioned in the introduction, we will mainly focus on systemic JIA (sJIA) and severe extended oligoarticular or polyarticular JIA. Notwithstanding this focus, it should be stressed that also oligoarticular JIA can be a serious disease burden for children, as the loss of function in even a single joint may lead to serious disability. Moreover, especially oligoarticular JIA patients are at a risk of developing uveitis as extra-articular complication or disease manifestation, which can threaten the vision in a significant percentage of children [7].

The most important reason for the focus on polyarticular and sJIA is pragmatic as, in general, the disease burden in JIA increases with the number of affected joints and with more severe systemic inflammation (as in sJIA). These patients have the highest risk of irreversible damage and long-term morbidity, and, consequently, they are most at risk of a lower quality of life. As such, these are the children with the greatest need for improved management.

New challenges in a changing landscape

The increased therapeutic possibilities of the past decade, resulting in improvement of arthritis in most children, change the way we define and classify severe JIA. A new description should thus not only consider active disease and joint damage but should take the chronicity of undergone treatment into account as well. For example, even as nowadays most patients can achieve clinically inactive disease, many of these patients will experience a relapse once treatment is tapered or stopped. This suggests that we achieve a state of disease suppression to a level that is clinically not detectable rather than a real cure. Even without the occurrence of irreversible joint damage through improved treatment, we do not know what the effects of continuous treatment with MTX or biologicals for 5, 10 or more years will be on the health of these children. Does it affect, for example, fertility? Or does it have an impact on the risks of cardiovascular events? Or even on the risk of developing a malignancy? In