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Editorial

Transition Between Treatments: What We Need to Know

Kirsten Minden[1] and Jens Klotsche[2]

Recent decades have seen the introduction of many new therapeutics into pediatric rheumatology practice, particularly biologic disease-modifying antirheumatic drugs (bDMARD). These advances are a result of the biotechnological revolution in the pharmaceutical industry, specific legislation for the development of pediatric medicines, and large international collaborative networks. The bDMARD have increased the probability of achieving challenging therapeutic goals such as remission in juvenile idiopathic arthritis (JIA). According to data from recent inception cohort studies in Canada and Germany, 75–81% of newly diagnosed JIA patients reached inactive disease during the first year of treatment, with 21–35% of cases receiving bDMARD[1,2]. There is growing evidence that rapid and aggressive disease control through early effective treatment is crucial for the further course and outcome of JIA[3,4,5]. For this reason, an international task force of 30 pediatric rheumatologists has recommended that a clinically inactive disease should be reached within the first 6 months of treatment by means of a treat-to-target approach[6]. If this therapeutic target, or at least minimal (or low) disease activity, has not been achieved, escalation of therapy (e.g., the use of one bDMARD or switching to another bDMARD) is recommended.

However, we are currently not in a position to predict drug outcomes, either at the start of treatment or at a time when treatment needs to be modified or escalated to maximize therapeutic outcomes. Despite the advances in treatment, managing JIA still often follows a trial-and-error principle. Patients with JIA may have to spend a lifetime testing medications that may not be effective in treating their condition[7]. With the ever-increasing number of medications, family and provider decision making is becoming increasingly complex, including the choice of the DMARD to switch to in case of treatment failure or intolerance.

Data on the most beneficial way to switch DMARD are still very limited. In this respect, the work of Melissa Mannion and her colleagues published in this issue of *The Journal of Rheumatology* is highly welcome[8]. The authors investigated the patterns and reasons for switching bDMARD in clinical practice in North America, using data from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry. They observed in a multicenter cohort of 1361 patients with nonsystemic JIA that within a median follow-up time of 30 months after the start of the first bDMARD, one in four patients switched to a second bDMARD and 8% to a third bDMARD. Ineffectiveness/disease flare was the most common reason for both the first and second bDMARD switch. Data from the period of 2008–2016 were considered, in which the median time to the first bDMARD switch became shorter (55 months in 2008, to 7 months in 2016). This suggests that pediatric rheumatologists were already practicing a steered treatment approach for JIA before the international recommendations for treating JIA to target were published. Most patients (94%) in the study by Mannion, *et al* had started treatment with a tumor necrosis factor inhibitor (TNFi), and the second bDMARD was also most frequently a TNFi[8]. In other countries around the world, switching to a second TNFi also seems to be the preferred choice when a first transition between bDMARD is required[9,10]. This is in contrast to the 2019 guideline of the American College of Rheumatology (ACR), according to which a switch to an alternative class of biologic (e.g., tocilizumab or abatacept) is conditionally recommended over switching to a second TNFi in the event of an inadequate response[11]. However, we do not really know yet if one or the other bDMARD is more effective in the first or second treatment course in nonsystemic JIA. Randomized head-to-head comparisons of bDMARD are lacking, and system-

[1]*K. Minden, MD, Epidemiology Unit, German Rheumatism Research Center Berlin, a Leibniz Institute, and Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin;* [2]*J. Klotsche, PhD, Epidemiology Unit, German Rheumatism Research Center Berlin, a Leibniz Institute, Berlin, Germany.*

KM receives honoraria for lectures from Abbvie, Pfizer, GSK, and Sanofi.

Address correspondence to Dr. K. Minden, Charité – Universitätsmedizin Berlin, Department of Rheumatology and Clinical Immunology, German Rheumatism Research Center, Epidemiology Unit, Chariteplatz 1, 10117 Berlin, Germany. Email: minden@drfz.de.

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atic reviews using indirect comparisons and data analysis from observational studies have not yet shown significant differences in the effectiveness of the different substances[12,13,14].

Mannion and colleagues have not investigated whether a TNFi or non-TNFi would be more effective as a second bDMARD[8]. However, such analysis was performed in a recently published British study based on data from two UK cohort studies [the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN) and the Biologics for Children with Rheumatic Diseases (BCRD) study][10]. In the British study, similar proportions of patients with polyarticular JIA, namely 23% and 5% switched to a second and third bDMARD, respectively, within a follow-up period of 2.2 years. Among 240 patients, 81% started a second TNFi and 19% a non-TNFi biologic after the initial TNFi had failed. The authors found that the choice of the second bDMARD (TNFi vs non-TNFi) did not affect the proportion of patients who achieved an ACR pediatric 90 response or minimal disease activity[10]. Therefore, they could not prove the superiority of a non-TNFi as second bDMARD after TNFi failure. Of course, this finding does not refute the ACR guideline, but rather calls for validation of this finding in further analyses with larger sample sizes.

Both studies on switching have not provided the reasons for the treatment choices. The presence of uveitis or other comorbidities, physician and patient preferences, treatment adherence, and antidrug antibodies (a relevant problem with monoclonal anti-TNF antibodies[15]) might have influenced the choice of drug. Whereas the transition between treatments with different modes of action (also known as swapping) and between different treatments with the same mode of action (also known as cycling) mainly occur due to medical reasons, the switching from originator to biosimilar occurs for nonmedical or economic reasons. With the increasing availability of biosimilars, the transition between different brands of the same drug will further increase the rate of switching. Theoretical concerns regarding this treatment transition include a possible loss of efficacy, changes in immunogenicity, and differences in safety profile compared to the biooriginator[16]. Despite these apprehensions, outcomes from randomized controlled trials in adults with rheumatic diseases and first real-life data on switching from a biooriginator to biosimilars have been reassuring[17]. However, published data for children and adolescents with rheumatic diseases are hardly available, and data collection on biosimilar effectiveness, safety, and immunogenicity in JIA is urgently needed.

Mannion and colleagues[8] have demonstrated that cohort studies, such as the CARRA registry, are valuable in describing trends in national prescription patterns. Such disease registries can also provide effectiveness and safety data on patients beginning treatment with a medication of interest and appropriate comparator patients during the same time period. This was highlighted at a stakeholder meeting in April 2018, when issues surrounding clinical trials and access to new medications for children and adolescents with JIA were discussed[7]. Participants pointed out that using large, prospective, observational disease-based registries allow to account for the unpredictable utilization of new medications, collect safety data for all drugs, and ensure that new drugs are tested over a long period of time and simultaneously with comparator drugs, thus providing meaningful information on the long-term and comparative effectiveness and safety of medications. In addition, it is now widely accepted that certain clinical questions cannot be considered in clinical trials due to their often short observation period, the inclusion of mostly high-risk patients, or ethical problems, but only in observational studies[18].

However, data from observational studies have to be carefully analyzed given the potential high risk of bias. One of the major sources of bias in observational studies is the so-called bias by indication in the comparison of treatment conditions. The treatment choice is by chance in clinical trials, whereas the treatment choice occurs naturally in cohort studies and is influenced by the clinical condition of the patient and personal preferences. This clearly limits the direct comparability of treatment groups in observational studies. Advanced statistical methods are available to adequately address the bias by indication in the analysis of data of observational studies, including propensity scores[10,19] or the Bayesian nonparametric causal inference method[4] in order to establish comparability between treatments.

Last but not least, observational cohort studies can help to better understand the basis for the observed interindividual variation in drug response and to identify predictors for response by characterizing clinical phenotypes, and recording clinical courses and treatment responses in a standardized way, along with collecting biosamples. Such approach holds the promise of identifying biomarkers that will guide clinicians in their efforts to tailor treatments and help optimize clinical response in patients with severe disease, but also prevent overly aggressive treatment in patients with mild disease[20].

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