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Editorial

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Risks of serious infections in children treated with biologic response-modifying drugs

Bacterial infection risk in children with juvenile idiopathic arthritis

This Editorial refers to Risk of serious bacterial infection associated with tumour necrosis factor-alpha inhibitors in children with juvenile idiopathic arthritis by Wan-Ju Lee *et al.* on pages. doi: 10.1093/rheumatology/kex049.

Lee *et al.* [1] report a 2.7-fold increase in the risk of serious bacterial infection for new use of TNF-α inhibitor (TNFi) monotherapy ($n = 482$) compared with new use of DMARD monotherapy ($n = 2013$), while controlling for corticosteroid use and other cofounders in a study cohort of commercially insured children with JIA. The authors analysed Truven Health MarketScan Commercial Claims and the Encounters database containing employer-based health insurance claims for enrolees and their dependents across the USA between 1 January 2009 and 31 December 2013. The new users had to have no previous use of either TNFis or DMARDs 6 months before the index date. During the mean follow-up of 255 days for the DMARD group and 307 days for the TNFi group, the authors observed 18 and 11 serious infections requiring hospitalization in 1405.4 and 404.9 total person-years for the DMARD and TNFi groups, respectively, resulting in crude rates of 1.28 (95% CI: 0.76–2.02) and 2.72 (95% CI: 1.36–4.86) serious infections per 100 person-years for these groups. The median time to infection was ∼90 days for both the TNFi and DMARD groups, with respiratory tract infections being the most common (36.4 and 33.3%, respectively), followed by infections of the digestive system; other organ systems, including blood and device-related infections; skin and skin structure and the genitourinary system.

Another similar study looking into the –>US Medicaid –>system contains data from 2000 to 2010. Comparing rates of hospitalized infection among children with JIA who were starting biologic response- modifying (BRM) agents –>*vs* those starting MTX without concurrent BRM use, Beukelman *et al.* [2] did not find an increased risk of infection with TNFi monotherapy or TNFi + –>MTX combination therapy compared with –>MTX alone. Corticosteroid treatment was one of the most significant risk factors for hospitalized infection in that study, as well as in the two other recently published studies on the association of significant infections with the use of TNFi in children with JIA from UK and German registries [3, 4]. Besides the higher treatment rate with glucocorticoids, another important factor for the significantly increased rate of medically important infections in patients treated with TNFi compared with –>MTX in the German study was the higher disease activity in these patients [4]. On the other hand, the increased rate of medically significant infections associated with TNFi compared with –>MTX was not sustained when the outcome was limited to serious infections requiring hospitalization or intravenous antibiotics in the UK study, where it was found that comorbid conditions at baseline and a longer history of disease for the TNFi cohort were important predisposing factors [3]. Similar to the report by Lee *et al.* [1], infections were reported to have occurred within the first 3–6 months following the initiation of treatment with TNFi [3].

As highlighted previously and discussed in the report by Lee *et al.* [1], monitoring the safety and reporting the side effects of BRM drugs, including severe infections and deaths, is one of the top priorities of the national and international patient registries and multicentre, international collaborative research consortiums such as PHARMACHILD, launched by the Paediatric Rheumatology European Society along with the Paediatric Rheumatology International Trials Organization in Europe, and the Enhanced Drug Safety Surveillance Project by the Childhood Arthritis and Rheumatology Research Alliance clinical network in the USA [5]. However imperfect, discrepant and seemingly conflicting, data from patient registries as well as from insurance and other administrative organizations are of crucial value, as there is a clear need for comparative studies addressing the safety of BRM drugs in JIA. These immunomodulatory agents have revolutionized the management of children with JIA over the last 15–20 years. But thus far the ultimate goal of a cure, or at least of lasting clinical remission off medication, remains unachievable in a significant percentage of patients [6], leaving them in need of prolonged treatment for many years/decades, usually combined with other anti-inflammatory and immunosuppressive agents.

Although the meta-analysis data on the safety of BRM in children are reassuring, there is good evidence of an association of the use of these drugs with an increased risk of severe infections, especially if combined with other immunosuppressive drugs [7, 8]. Even by selectively targeting cytokines and inflammatory pathways, the immunomodulatory effects of many BRMs are to some extent reproducing the experiments of nature, whereby a vital part of the innate or adaptive immune response is impaired by a single genetic defect in patients with rare primary immunodeficiency disorders (PIDs) [9]. We can and should use the knowledge from the experience gained by studying and caring for patients with these rare PIDs to predict the likely result of

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further immune dysregulation caused by targeted modulation of the already diseased immune system of children with JIA. For example, and relevant to the report by Lee *et al.* [1], blocking TNF function with a TNFi mimics the rare PIDs, affecting nuclear factor κB essential modulator and nuclear factor κB inhibitor alpha function, leading to grossly impaired cellular responses to TNF and other cytokines. As a result, due to the impaired TNF-dependent inflammatory pathway, patients with these disorders suffer not only from increased susceptibility to infections caused by mycobacteria and fungi, highlighting the crucial role TNF plays in defence against intracellular organisms, but also infections caused by viruses and other bacteria [9, 10].

The worries about real long-term side effects, including risks of autoimmunity and malignancy, but especially serious infections and significant mortality risk from severe infections, are the reality that clinicians, patients and their parents have to be aware of [7–11].

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