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MEETING REPORT

Annual European Congress of Rheumatology

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The Annual European Congress of Rheumatology is one of the largest rheumatology congresses in the world, providing a forum for the exchange of the latest scientific, clinical and patient-focussed research and information. The 20th Annual Congress was jointly organized with the Paediatric Rheumatology Society (PReS) for the first time. The meeting attracted 14,000 delegates from more than 120 countries. Among the 125 sessions and poster tours across the spectrum of rheumatic and musculoskeletal diseases, there were 14 devoted to pediatric rheumatology. This Meeting Report provides a brief summary of some of the new research and drug developments for pediatric rheumatology that were presented at the meeting.

1 Juvenile Idiopathic Arthritis (JIA)

1.1 Tapering Canakinumab Treatment in JIA

Professor Pierre Quartier presented preliminary data from a phase 3b/4 study investigating the safety and efficacy of two canakinumab tapering regimens (NCT02296424) in patients with systemic juvenile idiopathic arthritis (sJIA) [1]. Part 1 of the study identified patients with inactive disease on subcutaneous (SC) canakinumab (4 mg/kg every 4 weeks [q4w]) who were also corticosteroid (CS) and methotrexate (MTX) free for at least 4 weeks. In part 2, these patients were randomized to either a three-step dose titration protocol (2 mg/kg q4w for 24 weeks, then 1 mg/kg q4w for 24 weeks then discontinued) or to dose prolongation (4 mg/kg q8w for 24 weeks, then 4 mg/kg q12w for 24 weeks then discontinued)—patients advanced to the next step if inactive disease was maintained for 24 weeks. At the end of the first step, 71% of patients in the dose reduction arm and 84% of patients in the dose prolongation arm maintained inactive disease; the proportions were 68.4% and 81.1%, respectively, at the end of step 2. Overall, however, only 25 of the total 75 patients (33.3%) in part 2 of the study successfully discontinued canakinumab and maintained inactive disease state for 24 weeks.

1.2 Anakinra Real-World Data

Like canakinumab, anakinra blocks IL-1 signalling. Dr. Claudia Bracaglia reported the results of a review of 56 consecutive sJIA patients treated at the Ospedale Pediatrico Bambino Gesù in Rome who had been treated with anakinra for at least 6 months [2]. Overall, 39 patients (69.6%) achieved clinically inactive disease (Wallace criteria). Importantly, of the patients who started on anakinra within two months of disease onset, 93.1% (27/29) had inactive disease off CS at 6 months compared with only 44.4% (12/27) of patients who started anakinra after 2 months ($p=0.0001$). No other patient or laboratory parameters examined were associated with the odds of response at 6 months. The data suggest there may be an early 'window of opportunity' for treating this disease.

1.3 Abatacept Sustained Response

Professor Hermine Brunner reported on the long-term maintenance of clinical response to abatacept in children with polyarticular-course JIA (pJIA) according to patient age [3]. In this sub-group analysis of a phase 3 study (NCT01844518), patients aged 2–5 years and those aged 6–17 years who achieved a clinical response to abatacept at 4 months were followed for up to two years. Overall, a sustained response (JIA-ACR70) was maintained in more than 75% of patients at month 21 (32/34 [94.1%] patients aged

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2–5 years and 69/91 [75.8%] patients aged 6–17). Among patients aged 6–17 years, prior biologic treatment was an important prognostic factor, and fewer pre-exposed patients achieved JIA-ACR70 (81.4% versus 57.1%, p = 0.072) or JADAS71 MDA (another measure of disease activity; 71.1% versus 36.8%, p = 0.032).

1.4 Safety of Etanercept

Etanercept is the most widely used anti-TNFα agent in pediatric rheumatology. Two oral presentations delved into registry data to address safety questions regarding the use of etanercept for JIA. Previous studies have suggested a link between etanercept use in JIA and the development of IBD. To further explore this, Dr. Roline Krol and co-workers interrogated the Pharmachild JIA registry and included data from 8309 JIA patients, of whom 47 were classified as having inflammatory bowel disease (IBD) or suspected IBD [4]. Age at onset of JIA was significantly higher in those patients who developed IBD (9.1 vs 7.1 years, p = 0.002), and the proportion of females was lower (48.9% versus 67.6%, p = 0.011). Enthesitis-related arthritis (ERA) was the JIA subtype in 19 (40.4%) of patients who developed IBD compared with only 11% in the non-IBD cohort. While detailed information about IBD onset was only available for a small proportion of patients (14/47), the data suggested that MTX use did not play a protective role.

In the second presentation, Dr. Jens Klotsche reported on the long-term safety profile of etanercept using data from the German BiKeR and JuMBO registries, the latter following patients from BiKeR into adulthood [5]. In total, 1765 JIA patients were exposed to etanercept in the registries (mean etanercept exposure, 4.2 years) including 518 patients who have been continuously treated with etanercept for 5 years. The rate of serious adverse events was 4.76 per 100 exposure years (EY), 6.97 per 100EY for infections and 1.03 per 100EY for serious infections. Autoimmune events (1.84 per 100EY) and other immune disorders (0.10 per 100EY) were also noted. Eleven malignancies were reported in patients ever exposed to etanercept (0.10 per 100 person-years); these occurred on average 12.1 years after onset of JIA. However, the data are difficult to interpret given the often multiple different treatments across the 10 or so years since treatment with DMARDs was initiated in these patients.

2 Emapalumab for Macrophage Activation Syndrome (MAS)

MAS, a secondary form of hemophagocytic lymphohistiocytosis (HLH), is a severe complication of JIA characterized by the uncontrolled proliferation of activated T cells and macrophages, which is driven largely by the overproduction of interferon γ (IFNγ). Professor Fabrizio De Benedetti reported on the European results of a study of emapalumab, an experimental monoclonal antibody that blocks IFNγ, in pediatric patients with MAS (ACR/EULAR criteria) and sJIA who had not responded adequately to high-dose CS (NCT03311854) [6]. Six patients were treated with emapalumab (initial dose 6 mg/kg followed by 3 mg/kg twice a week for up to 4 weeks). Four of the six patients achieved a complete response by the end of treatment, and all six by week 8, with successful CS weaning in all patients. Laboratory analysis demonstrated the rapid neutralization of IFNγ and deactivation of T cells (as determined by CXCL9 and sIL-2R levels, respectively). Overall, treatment was well tolerated in these highly refractory patients; there was one case of CMV reactivation that resolved with treatment. Emapalumab was approved in April 2019 in the US for the treatment of primary HLH in paediatric and adult patients with refractory, recurrent or progressive disease or intolerance to conventional HLH therapy.

3 Subcutaneous Tocilizumab for JIA-Associated Uveitis

In this open-label, investigator-initiated study, reported by Professor Athimalaipet Ramanan in the late-breaking abstract session, JIA patients with active uveitis despite anti-TNFα treatment in combination with MTX were treated with SC tocilizumab for 12 weeks [7]. The primary outcome was treatment response at 12 weeks (according to SUN criteria; a 2 point reduction in inflammation or a decrease to 0); of 21 patients treated, 7 (33.3%) demonstrated a complete response and post-hoc analysis indicated that a further 4 patients achieved a partial response (1 point reduction) at week 12. Safety results were consistent with known profile of tocilizumab and there were no reported serious AEs.

4 Safety of Live Attenuated Vaccines in Pediatric Rheumatic Diseases

Safe and effective vaccination is important for all children, including those living with rheumatic diseases. Current EULAR guidelines, however, recommend withholding live-attenuated vaccines in patients on high-dose immunosuppressive regimens, including biologics, until more evidence is available given the theoretical risk of infection by the vaccine strain(s) [8]. Nevertheless, the guidelines do recognize that live-attenuated vaccines can be given on a case-by-case basis; indeed, given the recent measles epidemics, many doctors do administer live-attenuated vaccines to children with rheumatic diseases who are on immunosuppressive treatment. To provide additional safety data on this topic,

Dr. Veronica Moshe Bergonzo and colleagues collected retrospective data on the use of MMR or MMRV booster vaccinations from 13 pediatric rheumatology centres across 10 countries [9]. Data were available for 234 patients, most of whom had JIA (n = 206; the remaining patients had a variety of conditions including dermatomyositis, systemic or localized scleroderma, or idiopathic uveitis); active disease was seen in around half of patients (low 38%, moderate 7% and high 2%). Of the 110 patients who received the MMR/V booster while on MTX, 3 reported mild, local AEs; of the 76 patients on MTX and an anti-TNFα biologic, 7 reported mild and transient AEs (4 local, 3 flu-like); and 1/39 patients receiving anti-TNFα alone reported fever. Other patients received booster vaccinations while on tocilizumab (n = 3), anakinra (n = 7) or canakinumab (n = 5). There were no reported vaccine-related infections. The data add to the body of evidence pointing to the safety of live-attenuated vaccines in children with rheumatic diseases who are on immunosuppressive treatment, including biologics. A large prospective study is planned by the PReS vaccination study group to increase further the level of evidence.

Compliance with Ethical Standards

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Conflict of interest Rod McNab is a salaried employee of Adis/Springer Nature and declares no relevant conflicts of interest.

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