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, and the 18th Annual Congress coincided with the 70th anniversary of EULAR (the European League Against Rheumatism), attracting over 14,000 delegates from more than 120 countries. There were 180 sessions and poster tours across the spectrum of rheumatic and musculoskeletal diseases. There was a significant focus on biologics for pediatric rheumatology conditions, and this is reflected in this Meeting Report, which provides a brief summary of some of the new research and drug developments for pediatric rheumatology that were presented at the meeting.

1 CRIB and CRADLE: minimal transfer of certolizumab pegol during pregnancy and lactation

Good management of active chronic inflammatory conditions before/during pregnancy and lactation is crucial to ensure the best fetal and maternal outcomes. A EULAR task force has published points to consider for the use of antirheumatic drugs in these situations [1]. Among the recommendations for the use of biologics, etanercept and certolizumab pegol may be considered for use throughout pregnancy, whereas the use of other anti-TNF α agents is limited to the first trimester; there is a paucity of data on

safe use of biologics with other methods of action during pregnancy.

Biologics are usually derived from IgG, which permits the active transport of those molecules with an IgG1 Fc portion across the placenta, mediated by the fetal Fc receptor. Transfer is low during the first trimester but increases thereafter. Certolizumab pegol lacks the Fc portion and has no active placental transfer. The results of the CRIB study (NCT02019602), presented by Prof. Xavier Mariette (University Hospitals of Paris-Sud, France), confirmed this in 16 pregnant women with chronic inflammatory diseases [11 with rheumatoid arthritis (RA), three with Crohn's disease (CD) and one each with psoriatic arthritis (PsA) or axial spondyloarthritis (AS)] using a highly-sensitive certolizumab-specific electrochemiluminescence immunoassay with tenfold greater sensitivity than the assay used in prior studies [2]. In the CRIB pharmacokinetic (PK) study, the women (≥ 30 weeks' gestation) were receiving a maintenance dose of certolizumab pegol, with the last dose given within 35 days of delivery. Drug concentrations were determined in blood samples collected from the mothers, umbilical cords, and infants at delivery and from infants at 4 and 8 weeks post-delivery. Median gestational age at birth was 39.9 weeks (range 37.7–41.7) and median weight was 3.3 kg (range 2.6–4.0). Maternal certolizumab pegol levels at delivery were within the expected therapeutic range. Data were available for 14 infants at delivery; 13 had no quantifiable drug (<0.032 $\mu\text{g/ml}$, the lower limit of quantitation) whereas one had 0.042 $\mu\text{g/ml}$ (infant:mother plasma ratio 0.09%). Certolizumab pegol was not detected in any infant at weeks 4 or 8. Of the evaluable placentas, three had quantifiable drug levels (max. 0.048 $\mu\text{g/ml}$). Infants of treated mothers had a similar safety profile to those of unexposed infants of a similar age. Thus, the data indicate that there is unlikely to

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be any in utero fetal exposure to certolizumab pegol. In an accompanying press release, Prof. Mariette noted “The results of this study support the continuation of CZP [certolizumab pegol] treatment during pregnancy when considered necessary to control disease activity,” concluding “However, there will of course still be the risk of the typical adverse effects associated with an anti-TNF α treatment, such as infection or an immune reaction, which could affect the outcome of the pregnancy”.

Results of the CRADLE study [NCT02154425], which evaluated certolizumab pegol in breast milk, were presented as a poster by Prof. Megan Clowse (Duke University Medical Center, Durham, NC, USA) [3]. Using the same sensitive assay as used in CRIB, the investigators demonstrated minimal to no transfer of certolizumab pegol into breast milk. The study involved 17 mothers on stable certolizumab pegol treatment for RA ($n = 7$), CD ($n = 5$), PsA ($n = 3$), or AS ($n = 2$). Milk was collected at 2-day intervals across a single dosing period. While at least one milk sample was positive for 13 of the 17 mothers, the maximum concentration was 0.076 $\mu\text{g/ml}$, and certolizumab pegol was below the lower limit of quantitation in 56% of all samples. The average daily infant dose ranged from 0 to 0.01 mg/kg/day and the median relative infant dose was 0.15%, well within the acceptable limit ($<10\%$), and there were no untoward safety issues in mothers or infants. Low transfer of anti-TNF α agents has been shown previously; nevertheless, the results of the CRADLE study were well received.

2 Heterogeneity in juvenile idiopathic arthritis (JIA)

An interesting Paediatric Rheumatology session on heterogeneity in JIA included overview talks from Prof. Rae Yeung (University of Toronto, Toronto, Ontario, Canada), Dr. Wilco de Jager (University Medical Center Utrecht, Utrecht, The Netherlands), and Dr. Alessandro Consolaro (Giannina Gaslini Institute, Genova, Italy) covering progress in defining JIA subtypes and understanding the clinical and biological processes underpinning them. Various aspects were presented, including using principal component analysis to define disease clusters, technical considerations for the analysis of biological samples (e.g., for cytokine profiling), and epidemiological insights into JIA heterogeneity being generated by the EPOCA study such as therapeutic disparities across different geographic areas. A key message from Dr. de Jager was the need to standardize the sampling and analysis methodology for biological samples to allow meaningful evaluation of data, particularly across multicenter studies. The effects of any ongoing drug treatment on these biological disease markers also needs to be better understood.

In an abstract presentation by Prof. Gerd Horneff (Asklepios Clinic, Sankt Augustin, Germany), the changing patterns of JIA patients treated with etanercept since 2000 were detailed [4]. Analysis of records from 2105 JIA patients treated with etanercept in the German BIKER registry between 2000 and 2016 has revealed some very positive changes over the years including earlier treatment of patients and less severe disease at baseline. In addition, patients received less concomitant medication, notably a reduction in baseline concomitant steroids from 53.2% of patients in 2000–2002 to 18.5% of patients in 2015–2016. The distribution of JIA subtypes treated with etanercept has also changed over the years as other treatment options have become available. Prof. Horneff noted that while clinical outcomes in terms of the number of patients achieving remission has increased, the rate of this increase has slowed in recent years, and a new target of disease remission may be required.

The final talk in this session, presented by Prof. Carine Wouters (University Hospitals, Leuven, Belgium) reported the results of a small phase 1 study (NCT01455701) that explored the tocilizumab dosing regimen for systemic JIA patients aged less than 2 years [5]. Intravenous (IV) tocilizumab was dosed open-label at 12 mg/kg every 2 weeks. This was the dosing regimen for patients who were aged ≥ 2 years and who weighed <30 kg in the TENDER study (NCT00642460), which led to the approval of tocilizumab for systemic JIA in patients ≥ 2 years of age [6]. Eleven infants (median age 16 months, median weight 10.4 kg) were enrolled. Patients had uncontrolled systemic JIA and symptoms for ≥ 1 month and had failed treatment with corticosteroids and NSAIDs. At week 12, PK parameters, estimated using population PK analysis, were comparable to the population of TENDER patients weighing <30 kg ($n = 38$). By week 12, ten patients had experienced 32 adverse events (most frequently infestations or infections) and four withdrew (three because of serious hypersensitivity); there were two cases of suspected macrophage-activation syndrome (based on laboratory measures). Exploratory pharmacodynamics and efficacy measures responded positively; soluble interleukin-6R levels increased, serum C-reactive protein and erythrocyte sedimentation rate values decreased, and the mean juvenile arthritis disease activity score (JADAS)-71 improved from 22.27 ± 10.09 at baseline to 3.66 ± 4.66 at day 71.

3 Basic and clinical science abstract session

There were three drug-related abstracts presented in this session, reporting on subcutaneous (SC) abatacept, golimumab versus tocilizumab in JIA-associated uveitis, and canakinumab in patients with periodic fevers.

IV abatacept is approved for use in patients with moderate to severely active polyarticular JIA (aged ≥ 2 years in the USA and ≥ 6 years in the EU). An SC formulation of abatacept has been developed, and its PK, efficacy, and safety were investigated in a phase 3 open-label study (NCT01844518) in 234 polyarticular JIA patients (aged 2–17 years) who had an insufficient response or intolerance to at least one conventional disease-modifying antirheumatic drug (DMARD) or TNF α inhibitor. Dr. Nicolino Ruperto (Giannina Gaslini Institute, Genova, Italy) presented the patient-reported outcomes for a subset of this population, those aged 6–17 years ($n = 173$) [7]. Just over a quarter of these patients had failed treatment on a prior biologic, and almost 80% were using methotrexate. The Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) decreased from 0.99 ± 0.69 at baseline to 0.61 ± 0.64 at week 16; approximately 50% of patients showed at least a minimally important improvement in this measure. Similarly the Parent Global Assessment of overall patient wellbeing (PaGA) improved significantly from baseline to week 16. Importantly, the mean number of parent or caregiver days off work more than halved from approximately 4 days/month at baseline to less than 2/month at week 16; the mean number of days taken off school by children also decreased from 3 to 0.9. Patients who achieved a pediatric ACR30 response at week 16 could continue abatacept for a further 20 months. Overall, 132 patients completed the full study, and full PK, safety, and efficacy results are expected later this year. The subcutaneous formulation of abatacept was recently approved by the US Food and Drug Administration (FDA) for use in pJIA patients aged ≥ 2 years old.

Refractory uveitis in patients with JIA is usually managed with anti-TNF α agents. Prof. Lucia Domínguez-Casas (Hospital Universitario Marqués de Valdecilla, Santander, Spain) reported the outcome of a small study comparing golimumab with tocilizumab in refractory uveitis cases who had failed conventional treatment with high-dose corticosteroids and at least one immunosuppressant drug and one TNF α inhibitor [8]. Overall, 33 patients were enrolled (61 affected eyes); 25 received tocilizumab (majority 8 mg/kg IV every 4 weeks) and eight received golimumab (50 mg SC every month). The baseline patient characteristics were similar across groups, including age (approximately 19 years of age) and number of prior biologic treatments (approximately two). Tocilizumab and golimumab appear to be equally safe and effective; there were no differences in efficacy outcomes (visual acuity, degree of intraocular inflammation, vitreous inflammation, and macular thickening) across 1 year of treatment in this refractory population. Further randomized, controlled studies may be warranted.

In the same session, Prof. Fabrizio de Benedetti (Ospedale Pediatrico Bambino Gesù, Rome, Italy) reported preliminary results from the CLUSTER study (NCT02059291) evaluating canakinumab for three periodic fever syndromes: colchicine-resistant familial Mediterranean fever (crFMF), hyper-IgD syndrome/mevalonate kinase deficiency (HIDS/MKD), and TNF receptor-associated periodic syndromes (TRAPS) [9]. Patients entered the treatment phase (canakinumab 150 mg SC or placebo every 4 weeks for 16 weeks) at the time of an active flare. In cases of non-response or new flare, the dose could be escalated up to 300 mg every 4 weeks. The odds ratio for resolution of the initial flare and no new flares up to week 16 for canakinumab versus placebo was approximately 24 for crFMF and nine for patients with HIDS/MKD or TRAPS. The study design also allowed for investigation of a long-term maintenance dose, where responders were re-randomized to receive placebo or canakinumab 150 mg every 8 weeks for a further 24 weeks. Approximately 50% of crFMF and TRAPS patients maintained disease control through week 40, whereas up-titration to 300 mg every 4 weeks was required in approximately 30% of HIDS/MKD patients and 10% in the other two cohorts. The majority of canakinumab-treated patients in all three cohorts achieved a PGA of <2 and normalization of CRP and serum amyloid A (SAA) levels during the maintenance phase. No unexpected safety issues were reported. Canakinumab was recently approved in the USA for these indications [10].

4 Summary and future meeting

There were several other interesting and informative pediatric sessions during the meeting, covering outcomes in JIA and transition from pediatric to adult care, for example, as well as very many poster presentations. Abstracts from this meeting and from previous years are available from <http://scientific.sparx-ip.net/archiveular/>. The 19th EULAR Annual Congress will be held in Amsterdam, The Netherlands, from 13 to 16 June 2018.

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