CHARACTERISTICS AND OUTCOMES OF PROSPECTIVELY REPORTED PREGNANCIES EXPOSED TO CERTOLIZUMAB PEGOL FROM A SAFETY DATABASE

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Objective: Certolizumab pegol (CZP) is indicated for the treatment of rheumatoid arthritis, Crohn’s disease, and psoriatic arthritis. To evaluate the reproductive outcomes of women exposed to CZP during pregnancy.

Methods: Prospective and retrospective data on maternal CZP exposure, including timing and duration, outcomes, comorbidities, and major malformations were extracted from the UCB Pharma safety database through 6 March 2017. This analysis was limited to prospective reports to avoid bias associated with retrospective submissions. Numbers of live births, miscarriages, elective abortions, stillbirths, and major congenital malformations were ascertained.

Results: From a total of 1541 maternal CZP-exposed pregnancies, 1137 were reported prospectively, of which 528 pregnancies (including 10 twin pregnancies) had 538 known outcomes: 459 live births (85%), 47 miscarriages (9%), 27 elective abortions (5%), and 5 stillbirths (1%) (figure 1). Of the 459 live births, 8 (2%) cases had 538 known outcomes: 459 live births (85%), 47 miscarriages (9%), 27 elective abortions (5%), and 5 stillbirths (1%) (figure 1). Of the 459 live births, 8 (2%) cases had known outcomes, 436 (83%) were exposed during the 1st trimester, when most organogenesis occurs; 201 pregnancies were exposed during the entire pregnancy.

Conclusions: This analysis represents the largest published cohort of pregnant women exposed to an anti-TNF for management of chronic inflammatory diseases. Analysis of pregnancy outcomes does not indicate a malformative effect of CZP compared to the EU general population (2%-3%), nor an increased risk of foetal death. These data are reassuring for women of childbearing age considering treatment with CZP; however, the ongoing collection of post-marketing surveillance data, including the ongoing MotherToBaby study from the Organisation of Teratology Information Specialists, will provide further important information.

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Do we still need biopsies to diagnose Sjögren’s and autoimmune myositis?

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Background: In addition to glomerular lesions, renal vascular involvement is an important prognostic marker of lupus nephritis (LN). Among patients with various vascular changes, individuals with thrombotic microangiopathy (TMA) present with severe clinical manifestations and have a high mortality.

Objectives: We sought to assess renalaloutcomes and response to anti-thrombotic treatmentin addition to conventional immunosuppression in patients with biopsy proven LN and TMA.

Methods: Clinical and renal histopathological data for 97 patients with biopsy-proven LN and TMA were retrospectively analysed. Antibody profiles, induction and maintenance therapies for LN, and anti-thrombotic treatments were collected. TMA lesions were classified into acute and chronic (table 1). A complete renal response (CR) was defined as proteinuria <0.5 g/24 hour and normal or near-
normal (within 10% of normal GFR if previously abnormal) GFR. Partial Response (PR) was defined as ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR. Renal outcomes were ascertained at one year post biopsy.

Results: The mean age of the patients was 38.9±15.2 years (range, 13–69 years). The study included 85 females (87.6%) and 12 males (12.4%). The clinical presentations were nephrotic syndrome, nephritic syndrome, and asymptomatic urinary abnormalities in 38 (39.2%), 20 (20.6%), and 39 (40.2%) patients, respectively. Nine patients were classified as Class III (9.3%, including 2 as Class III +IV), 82 as Class IV (84.5%), 10 as Class IV-segmental/IV-S (10.3%) and 72 as Class IV-global (IV-G) (74.2%), including 4 as Class IV-G+V and 6 as Class V (6.2%). Forty-two (43%) patients presented with acute and 55 (57%) with features of chronic TMA. All patients had received treatment with standard immunosuppressants (55% mycophenolate, 39% cyclophosphamide, 6% other regimen) and steroids.

Abstract OP0201 – Table 1

<table>
<thead>
<tr>
<th>Acute TMA features</th>
<th>Chronic TMA features</th>
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</thead>
<tbody>
<tr>
<td>Endothelial swelling with partial or complete occlusion of lumina;</td>
<td>Capillary wall thickening with double contours;</td>
</tr>
<tr>
<td>Microthrombi, focal or global;</td>
<td>Organizing capillary thrombi;</td>
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<tr>
<td>Fragmented RBC on glomerular subendothelial space and</td>
<td>Glomerular ischemic collapse with other alveolar occlusion;</td>
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<tr>
<td>mesangial areas;</td>
<td>Segmental/global glomerular alteration;</td>
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<tr>
<td>Segments, focal,</td>
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<tr>
<td>Segmental/glomerular congestion with efflux</td>
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<td>Arteriolar occlusion</td>
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</table>

At 12 months, CR was observed in 37 patients (38.1%), PR in 22 (22.6%) and no response in 38 (39.1%). Sixty-one patients (62.9%) were antiphospholipid positive (aPL) and 37 (38.1%) received anticoagulation with vitamin-K antagonist (VKA) and/or heparins. Presence of aPLs (OR, 2.4; 95% confidence interval (CI), 1.2–7.3; p=0.03), anti-DNA positivity (OR, 12.8; 95% CI: 3.0 to 71.3; p<0.002), and chronic features of TMA (OR, 3.0; 95% CI: 1.2 to 7.5; p=0.04) were all found to be associated with no response. When limiting the analysis to aPL positive patients, after adjusting for type of immunosuppressant therapy and LN class on biopsy, variables that were significantly associated with CR +PR were features of acute TMA rather than chronic (OR, 8.62; 95% CI: 1.4 to 97.1; p=0.03) and the use of VKA/heparins (OR, 2.1; 95% CI: 1.02–16.2; p=0.046).

Conclusions: In patients with concomitant LN and TMA, the presence of aPL and chronic features of TMA were associated with poorer renal outcomes. In patients with concomitant LN and TMA, the presence of aPL and chronic features of TMA were associated with poorer renal outcomes. In patients with concomitant LN and TMA, the presence of aPL and chronic features of TMA were associated with poorer renal outcomes. In patients with concomitant LN and TMA, the presence of aPL and chronic features of TMA were associated with poorer renal outcomes. In patients with concomitant LN and TMA, the presence of aPL and chronic features of TMA were associated with poorer renal outcomes. In patients with concomitant LN and TMA, the presence of aPL and chronic features of TMA were associated with poorer renal outcomes.

Disclosure of Interest: None declared


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How monogenetic autoinflammatory diseases help to understand and treat rheumatic diseases

GENE EXPRESSION PROFILES IN PRIMARY SJÖGREN’S SYNDROME WITH AND WITHOUT SYSTEMIC MANIFESTATIONS

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Background: Different phenotypes characterise the clinical spectrum of primary Sjögren’s syndrome (SjS). Patients with a clinical expression limited to glandular features (GFs) are classically distinguished from patients with extra-glandular manifestations (EGMs). The former patients often complain higher level of fatigue and widespread pain (WP). (Segal et al. 2013) This suggests that gene expression pattern may be different in the two subgroups.

Objectives: To investigate the differences of gene expression in SjS patients with GFs and in those with EGMs.

Methods: Nineteen patients with SjS were selected for the study. Gene expression in peripheral blood mononuclear cells (PBMCs) was analysed in 4 patients with EGMs and 4 patients with GFs alone using Clariom D human Affymetrix gene chip (Affymetrix, Santa Clara, CA, USA), and compared to that found in healthy controls. Differences in gene expression were evaluated by analysis of variance (ANOVA) and Step-Up FDR-controlling procedure, being FDR corrected p value <0.01 and fold change >2 considered as statistically significant.

Validation of the gene overexpression was performed by quantitative Real Time (qRT)-PCR in PBMCs from all the selected SjS patients, using the ΔΔCt method for comparing relative fold expression differences.

Results: All the enrolled SjS patients (18 females and 1 male) had a positive lip biopsy, while anti-SSA/Ro antibodies were detected in 10/11 and 6/8 of the patients with EGMs and with GFs alone, respectively. ESSDAI value ranged from 7 to 55 in patients with EGMs (median 17), and from 0 to 2 in patients with GFs alone (median 1).

In both types of patients, the functional analysis of the two transcriptomes showed a large number (>1000) of modulated genes that are involved in the well-known pathological processes of SjS, i.e., apoptosis, inflammatory response, immune response, type I and type II interferons, and Toll-like receptors signalling. Genes modulated only in patient with EGMs showed a significant enrichment of the biological processes associated with immune response (79% of all enriched processes) and, namely, of the molecular pathways related to B cell activation. The analysis of the transcripts expressed only in patients with GFs alone showed instead a preponderant enrichment in different metabolic processes (43%) and in processes associated with the central perception of the stimuli. Indeed, genes involved in sensory perception and in nociceptive signals (i.e., ANPEP, TRNF1, P2RY1, IFNG) were modulated exclusively in patients with GFs alone. The significant differential expression of selected genes in the two SjS subgroups was confirmed by the qRT-PCR analysis.

Conclusions: These data indicate that in SjS patients with GFs alone a dysregulation of pain pathways (namely beta-adrenergic receptor and Notch signalling) may play a role in the development of WP that is common in this subset of patients. The biological mechanisms triggering the activation of these genes remain to be completely clarified.

Disclosure of Interest: None declared


SAFETY AND EFFICACY OF INTRAVENOUS ADMINISTRATION OF BONE-MARROW DERIVED MESENCHYAL STROMAL CELLS IN THERAPY REFRACTORY JUVENILE IDIOPATHIC ARTHRITIS PATIENTS, A PHASE II/IIA PILOT-STUDY


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Objectives: To compare the total number of adverse events (AE) before and after mesenchymal stromal cell (MSC) infusion in refractory JIA and to evaluate its effectiveness.

Methods: Single-centre Phase II/IIa, open label intervention study in JIA patients previously failing all biologicals registered for their diagnosis. Six patients will receive 2 million/kg intravenous infusions of allogeneic bone-marrow derived MSC. In case of ACR-Ped30-response but subsequent loss of response one and maximal two repeated infusions are allowed.

Results: Six JIA patients with 9.2 years median disease duration, still active arthritis and damage were included. All had failed methotrexate, corticosteroids and median 5 different biologicals. MSC were administered twice in 3 patients. No acute infusion reactions were observed and a lower post-treatment than pre-treatment incidence in AE’s was found. The one SjIA patient had again an evolving macrophage activation syndrome, 9 weeks after tocilizumab discontinuation and 7 weeks post-MSC infusion.

Eight weeks after one MSC infusion, 4 patients showed less active joints, 5 patients improved in many clinical parameters and inflammatory parameters decreased in 3/4. After 1 year, we found significantly lower active joint counts,