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Oral presentation 911:

Efficacy and Safety of Tocilizumab in Patients with Giant Cell Arteritis: Primary and Secondary Outcomes from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial (GiACTA Study)

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Background/Purpose: The efficacy and safety of tocilizumab (TCZ), an IL-6 receptor-alpha inhibitor, was evaluated in patients with giant cell arteritis (GCA) in GiACTA, a randomized, double-blind, placebo-controlled trial with blinded glucocorticoid regimens of variable dose and duration (Int J Rheumatol. 2013:912562). Data up to week 52, the time of primary outcome measurement, are presented.

Methods: Patients aged ≥50 years had active GCA previously confirmed by temporal artery biopsy or cross-sectional imaging and documented acute-phase reactant elevation attributable to GCA. Randomization was stratified by baseline prednisone dose (≤30 or >30 mg/day). Patients were randomized 1:1:2:1 to 4 groups: A, short-course prednisone (26-week prednisone taper + weekly subcutaneous [SC] placebo); B, long-course prednisone (52-week prednisone taper + weekly SC placebo); C, weekly SC TCZ 162 mg + 26-week prednisone taper; D, every other week SC TCZ 162 mg + 26-week prednisone taper. The baseline prednisone dose (20-60 mg/day) was selected by the investigator. Prednisone doses <20 mg/day were blinded. Patients who flared or could not adhere to the protocol-defined tapering schedule received open-label prednisone escape therapy but continued on double-blind TCZ/placebo. Sustained remission was defined at week 52 as the absence of flare and normalization of C-reactive protein after week 12, combined with adherence to the protocol-defined prednisone taper. The primary and key secondary end point was the proportion of patients in sustained remission, comparing both TCZ groups (C, D) with the short-course prednisone group (A) and with the long-course prednisone group (B), respectively, at a significance level of 0.005. A dose hierarchy of statistical testing was implemented. Cumulative prednisone exposure was a secondary end point.

Results: Of 251 patients randomized, the mean ± SD age was 69 ± 8.2 years, and 75% were female. In the primary comparison, 56% of patients in the weekly TCZ group and 53.1% in the every other week TCZ group achieved sustained remission at 12 months compared to only 14% in the short-course prednisone group (p < 0.0001). In the key secondary efficacy comparison, the percentage of patients in sustained remission in each TCZ group was also superior to that of patients in the long-course prednisone group (17.6%) (p ≤ 0.0002). The median cumulative steroid exposure in both TCZ groups was less than half that of those in the long-course prednisone group (Table). The incidence of adverse events was similar among the 4 treatment arms. No deaths and no new vision loss occurred over the period of observation.

Conclusion: TCZ plus a 26-week prednisone taper was superior to both short- and long-course prednisone tapers for the achievement of sustained remission at 52 weeks. The addition of TCZ to prednisone also led to a substantial reduction in the cumulative prednisone doses required to control GCA.
### Table. Efficacy and Safety During GIACTA Part 1

<table>
<thead>
<tr>
<th>Patients in sustained remission at 52 weeks, n (%)</th>
<th>A) Short-course prednisone n = 50</th>
<th>B) Long prednisone n = 51</th>
<th>C) Weekly SC TCZ n = 100</th>
<th>D) Every other week SC TCZ n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ groups vs short-course prednisone</td>
<td>7 (14.0)</td>
<td>9 (17.6)</td>
<td>56 (56.0)</td>
<td>26 (53.1)</td>
</tr>
<tr>
<td>Unadjusted difference in proportion of responders (99.5% CI)</td>
<td>–</td>
<td>–</td>
<td>42.0 (18.0, 66.0)</td>
<td>39.1 (12.5, 65.7)</td>
</tr>
<tr>
<td>TCZ groups vs long-course prednisone *</td>
<td>–</td>
<td>–</td>
<td>38.4 (17.9, 58.8)</td>
<td>35.4 (10.4, 60.4)</td>
</tr>
<tr>
<td>Unadjusted difference in proportion of responders (99.5% CI)</td>
<td>–</td>
<td>–</td>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Cumulative CS dose, median (min-max)</td>
<td>3296.00 (932.0-9777.5)</td>
<td>3817.50 (822.5-10697.5)</td>
<td>1862.00 (630.0-6602.5)</td>
<td>1862.00 (295.0-9912.5)</td>
</tr>
<tr>
<td>AEs</td>
<td>48 (96.0)</td>
<td>47 (92.2)</td>
<td>98 (98.8)</td>
<td>47 (95.9)</td>
</tr>
<tr>
<td>Patients with event, n (%)</td>
<td>6 (12.0)</td>
<td>5 (9.8)</td>
<td>15 (15.0)</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>2 (4.0)</td>
<td>0</td>
<td>7 (7.0)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>SAEs</td>
<td>11 (22.0)</td>
<td>13 (25.5)</td>
<td>15 (15.0)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>Infection SAEs</td>
<td>2 (4.0)</td>
<td>6 (11.8)</td>
<td>7 (7.0)</td>
<td>2 (4.1)</td>
</tr>
</tbody>
</table>

**AE**, adverse event; **CI**, confidence interval; **SAE**, serious adverse event.

Patients who receive escape therapy, withdraw, or do not achieve remission by week 12 are classified as nonresponders.

Patients who have 2 consecutive CRP elevations >1 mg/dL from week 12 or have >100 mg additional steroids from week 12 are classified as nonresponders.

*p* values for superiority of the primary and key secondary end points were compared to a significance level of 0.005 to account for multiplicity; all other secondary end points are compared to 0.01.

*p* values for superiority calculated using a Cochran-Mantel-Haenszel test adjusting for starting prednisone dose (≤30 mg/day, <22.5 was used to compare TCZ groups with long-course prednisone group using 99.5% CIs.
Oral presentation 977:

Tocilizumab as an Add-on Therapy to Glucocorticoids during the First 3 Months of Treatment of Giant Cell Arteritis: Results of a French Multicenter Prospective Open-Label Study

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Background/Purpose: Giant cell arteritis (GCA) is a large-vessel vasculitis usually treated with glucocorticoids (GC). GC are effective but responsible for substantial morbidity and mortality. Tocilizumab (TCZ) is a humanized monoclonal antibody against interleukin-6 receptor (IL-6R) that has recently been shown to be effective for the induction and maintenance of remission in GCA when used monthly for 1 year (1). However, data concerning the course of GCA after TCZ discontinuation are lacking and the optimal duration of this expensive immunosuppressive therapy in GCA is unknown. Our study therefore aimed to evaluate TCZ as an add-on therapy to GC during the first 3 months of GCA treatment (2).

Methods: Patients affected by GCA, as defined by the 1990 ACR criteria and a positive temporal artery biopsy (TAB) or CT-scan or PET-scan-proven aortitis were included in this French multicenter prospective open-label study. GC were started at 0.7 mg/Kg/day and then tapered according to a standardized protocol (2) with the aim to reach 0.1 mg/Kg/day at week 24 (W24). All patients received 4 infusions of TCZ (8 mg/Kg/4 weeks) after inclusion (W0, W4, W8 and W12). The primary endpoint was the percentage of patients in remission with a dose of prednisone ≤0.1 mg/Kg/day at W26. Patients were followed for 26 weeks and data about relapses and adverse events were prospectively recorded. Quantitative data are presented as mean±SD. This trial was registered with ClinicalTrials.gov, number NCT01910038.

Results: Twenty patients (15 women, 19 new-onset GCA) were included in this study between March 2014 and June 2015. Age at diagnosis was 72.6±7.6 years. TAB was positive in 17/19 (90%) patients and 7/16 (44%) had aortitis. Remission was obtained in all the cases, at W4 for 18/20 (90%) patients and at W8 and W12 for the two others. At W26 (14 weeks after last TCZ infusion), 5 patients (25%) had relapsed, 24.5±2.3 weeks after inclusion and at a mean dose of prednisone of 6.4±2.1 mg/day. One of these relapses was limited to a slight increase in the CRP (10 mg/L) and fibrinogen (4.6 g/L) level at W24; GC were briefly increased but the primary endpoint was reached at W26 without subsequent relapse. One patient died suddenly at W26 and was not considered to have reached the primary endpoint in the final analysis. Finally, 15 (75%) patients met the primary endpoint at W26, which is higher than previously reported with the same GC tapering i.e. 50% in the placebo group from the HECTHOR trial (2). Prednisone cumulative dose at W26 was 3,524±811 mg. After 26 weeks, 60 adverse events were reported in 19 patients and 20 were considered directly related to the study, the most common being hypercholesterolemia (n=8), infections (n=7 [3 before week 16]), and hepatic cytolysis (n=1).

Conclusion: Four TCZ infusions as an add-on therapy to GC for GCA treatment allowed rapid GC tapering and persistent remission with a low dose of GC (0.1 mg/Kg/day) after 6 months of follow-up. However, relapses can occur after TCZ discontinuation and further studies are needed to identify predictive factor of relapse after TCZ discontinuation.

**Oral presentation 3183:**
**Tocilizumab for the Treatment of Giant Cell Arteritis - MR-Angiography Results from the First Randomized Placebo-Controlled Trial**

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¹University of Bern, Bern, Switzerland, ²University Hospital Bern, Bern, Switzerland

**Background/Purpose:** As published in The Lancet online, March 4, 2016, the first randomized, placebo-controlled trial (RCT) of tocilizumab (TCZ) in giant cell arteritis (GCA) showed clinical efficacy of the anti-IL-6 receptor biologic agent in the induction and maintenance of remission for up to 52 weeks. However, very little is known about inflammatory signals in the vessel walls of TCZ-treated patients. Therefore, the aim of this analysis was to evaluate the inflammation of the vessel wall as seen on magnetic resonance angiograms (MRAs) during the RCT and to compare the signals in the two treatment arms.

**Methods:** In this single-center RCT participants who satisfied the 1990 American College of Rheumatology criteria were randomly assigned in a 2:1 ratio to receive either TCZ (8 mg/kg of body weight) + glucocorticoids (GC) or placebo + GC. Participants received infusions at 4-weekly intervals for 52 weeks, and GC were started at 1 mg/kg/d and then tapered down to zero. GCA was proven by positive temporal artery biopsy and/or assessed as large vessel vasculitis by MRA using a score 0 to 3; 0= no mural thickening (vessel wall diameter < 0.6 mm), no enhancement; 1= no thickening, slight mural enhancement; 2= mural thickening (> 0.6 mm), significant mural enhancement; 3= strong thickening (> 0.7 mm), strong mural and perivascular enhancement. Scores 2 and 3 were considered to represent active mural inflammation. The MRAs were analyzed by two experienced radiologists who were blinded to treatment allocation. If positive at inclusion, MRA was repeated after 3 months and at end of the study. The primary outcome for this analysis was the number of patients with complete remission on MRA based on the vasculitis score at week 12 (GC dose of 0.1 mg/kg/d). The secondary outcome was the number of patients with complete MRA remission at week 52 and the change in the vasculitis score.

**Results:** Twenty-eight of 30 randomized patients underwent baseline MRA, 20 in the TCZ + GC group and 8 in the placebo + GC group. 11 MRAs at baseline (9 in the TCZ + GC group and 2 in the placebo + GC group) had no signs of vasculitis. At week 12, MRAs were performed in 9 patients in the TCZ + GC group, all of whom were in clinical remission, and 4 patients in the placebo + GC group, 2 of whom were in remission. Three (33%) patients in the TCZ + GC group were in complete MRA remission, compared to 1 (25%) in the placebo + GC group. At week 52, there was additional improvement, but no complete remission, on MRA in 3 participants in the TCZ + GC group, resulting in a median change in the vasculitis score of -1.0, and no improvement in the remaining 2 participants in the placebo + GC group, resulting in a median change in the vasculitis score of -0.5.

**Conclusion:** TCZ induces and sustains clinical remission of GCA but does not completely suppress MR signals of vessel inflammation. Whether these signals are of prognostic importance remains to be determined and should be further evaluated in long-term studies.
Poster 867:
Termination of Tocilizumab-Treatment in Giant Cell Arteritis: Follow-up of Patients after the RCT
(ClinicalTrials.gov registration number: NCT01450137)

Sabine Adler¹, Stephan Reichenbach², Stefan Kuchen², Felix Wermelinger¹, Diana Dan¹, Michael Seitz² and Peter M. Villiger³,
¹University Hospital Bern, Bern, Switzerland, ²University of Bern, Bern, Switzerland

Background/Purpose: As published in The Lancet online, March 4, 2016, the first RCT about tocilizumab (TCZ) in GCA showed clinical efficacy of the anti-IL-6 biologic agent in the induction and maintenance of remission for up to 52 weeks. This study analyzed the long-term outcome after termination of the RCT.

Methods: 30 patients with Giant Cell Arteritis (GCA) were randomized in this RCT in a 2:1 ratio into receiving intravenously (i.v.) TCZ 8mg/kg bodyweight plus Glucocorticoids (GC) or Placebo (PB) plus GC. They received infusions in 4-weekly intervals for 52 weeks. Thereafter TCZ medication was stopped, further treatment was prescribed by the treating physicians, patients were followed up clinically.

Results: By week 52 of the RCT all patients of the TCZ arms were in sustained complete remission, of these 18 without GC co-medication. 2/20 patients received GC after the last infusion due to premature stop of TCZ, one patient with Stevens-Johnson-syndrome and one with diverticulitis. Median follow-up time was 12.5 months (range 3-32). After the last infusion of TCZ 11/20 patients relapsed with a median time to relapse of 5 months (range 2-14). In the placebo arm all but one patient relapsed and/or continued GC treatment. Remarkably, 1/10 PB patients remained in remission throughout the study and was without medication at last follow-up, 10 months after the end of study. None of the relapsing patients experienced blindness, aortic rupture, aortic stenosis or other major vascular complications. In case of relapse, dose of GC was 1mg/kg bodyweight in signs of major relapse and 20-40 mg/d in minor relapse according to the average dose during the study period that was sufficient to control symptoms in PB patients prior to relapse. Additionally, in 6/11 TCZ patients relapsing after the last study infusion, TCZ was re-administered with 8mg/kg bodyweight i.v. in monthly intervals after a median time of 6.5 months (range 3-14). In 2/6 patients with TCZ re-introduction, TCZ was stopped after 4 and 6 months, respectively, with lasting remission. In 1/6 patients TCZ was again given for 2 months, stopped in remission yet had to be re-introduced 6 months later due to a second relapse.

Conclusion: Clinical and serologic remission in response to TCZ for 52 weeks does not result in relapse-free survival after termination of treatment. Although IL-6 blockade using TCZ controls clinical disease, it may not control pathogenesis in all cases. The fact that 45% of patients remained in lasting remission may help to design treatment protocols to determine appropriate maintenance dosage regimens of TCZ after achievement of remission.

Figure 1.
Poster 2104: Treatment with Tocilizumab Decreases CXCL13 Expression in Cultured Temporal Arteries from Patients with Giant Cell Arteritis

Nekane Terrades-Garcia, Joana Daradoumis, Ester Planas-Rigol, Marc Corbera-Bellalta, Sergio Prieto-González, Georgina Espígol-Frigolé and Maria C. Cid, Hospital Clínic. University of Barcelona. IDIBAPS, Barcelona, Spain

Background/Purpose: IL-6 has been considered a biomarker of disease activity in GCA and a potential therapeutic target. However, the functional role of IL-6 in GCA has not been explored. IL-6 has important roles in B cell homeostasis and Th17 differentiation as well as in driving the acute-phase response which underlines systemic symptoms in GCA. Blocking IL-6 receptor with tocilizumab (TCZ) has shown efficacy in maintaining remission in case series of refractory patients with GCA and in a recently published randomized clinical trial (Villiger PM et al Lancet 2016). We hypothesized that TCZ may disturb B cell homeostasis and interfere with tertiary lymphoid organ (TLO) formation. To explore TLO formation in GCA arteries and to investigate the impact of IL-6R blockade with TCZ on TLO markers in ex-vivo cultured arteries from patients with GCA.

Methods: Formation of TLO was explored in temporal artery biopsies from patients with GCA by immunofluorescence using CD20 (B cell marker) and CD21 (follicular dendritic cell marker). Expression of TLO markers CXCL13, LTα and LTβ was assessed by quantitative real-time PCR in temporal artery biopsies from 13 patients with GCA and 13 control individuals. To investigate the effect of TCZ, temporal arteries from 13 GCA patients and 8 controls were cultured on 3D matrix (Matrigel) with or without TCZ (purchased from Roche) at 10mg/ml or IgG isotype control at the same concentration. After 5-day culture, expression of CXCL13, LTα and LTβ was assessed by quantitative RT-PCR. Other pro-inflammatory (IL-1β) survival (BCL-6, BAFF) or remodelling (TGFβ) molecules relevant to GCA pathogenesis were also assessed.

Results: B cell clusters intermingled with follicular dendritic cells were identified in temporal artery biopsies from patients with GCA, particularly in the adventitial layer. mRNA expression of CXCL13 (16.93 vs 7.10 relative units, p=0.001), LTα (16.82 vs 6.18, p=0.0001) and LTβ (16.75 vs 9.54, p=0.014) was significantly higher in temporal arteries from GCA patients compared to healthy controls. After 5-day culture, TCZ selectively induced a significantly decrease in CXCL13 mRNA expression in cultured arteries (p=0.023). No significant changes in LTα, LTβ, IL-1β, BCL-6, BAFF or TGFβ expression were observed upon TCZ treatment.

Conclusion: Treatment with TCZ elicits a significant and selective reduction of CXCL13 expression in temporal artery lesions from patients with GCA. Disruption of B cell homeostasis may partially account for the therapeutic effects of TCZ in patients with GCA. Supported by SAF 2014/57708-R
Poster 882: Polymyalgia Rheumatica Activity Score without C-Reactive Protein (TENOR Study)

Valérie Devauchelle, Department of Rheumatology, Brest University Hospital, Brest, France; Lea Saraux, CHU Brest, Brest, France; Jean-Marie Berthelot, Nantes University Hospital, Nantes, France; Divi CorneC, Brest Occidentale University, Brest, France; Thierry Marhadour, CHU La Cavale Blanche, Brest, France; Sandrine Jousse-Joulin, CHU la Cavale Blanche, Brest, France; Michel De Bandt, CHU Fort de France, Fort de France, France; Maelenn Gouillou, CHU la Cavale Blanche-Institut National de la Santé et de la Recherche Médicale (INSERM), Brest, France and Alain Saraux, CHU Brest et Université Bretagne Occidentale, Brest, France

Background/Purpose: Disease activity of polymyalgia rheumatica (PMR) (1, 2) may be evaluated using the PMR activity score (PMR-AS). For patients without measure of CRP, or patients having a treatment modifying its measure (i.e. anti-IL6), the PMR-AS could be unmeasurable or biased. Three options should be suggested: 1- to use ESR instead CRP but anti IL6 may also modify ESR; 2- to use PMR-AS without CRP (clin-PMR-AS) as an item but its validation is mandatory; 3- to replace CRP by a virtual value imputed on the basis of the other parameters (CRP-imputed-PMR-AS). Our goal was to build a PMR-AS using imputed value of CRP.

Methods: We used two independent cohorts of patients: the CRI cohort (137 visits of 89 PMR patients without any treatment or treated by corticosteroids) (2) and the TENOR cohort (20 patients, 20 visit at inclusion without any treatment, 20 visit at W4, 8, 12 during tocilizumab infusions, and 20 visit at 16, 20 and 24 weeks with treatment by steroids) (2). In the CRI cohort, we evaluated the correlation (Spearman) between the items of the PMR-AS to define which of them may be the best to perform an imputation of CRP. Then we built a scatter plot representing PMR-AS and clin-PMR-AS. Their correlation could be represented by an equation y=ax+b. We verified that the CRP-imputed-PMR-AS in patients of the TENOR cohort without treatment by tocilizumab gave a good correlation with PMR-AS with CRP. Finally, we evaluated the difference of PMR-AS without CRP and the CRP-imputed-PMR-AS in the TENOR cohort during the visit 4, 8 and 12.

Results: On the CRI cohort, we observed a good correlation between the items of the PMR-AS, the clin-PMR-AS and PMT-AS. Agreement between PMR-AS with and without CRP was excellent (using cut off 0-7-17-∞; only 5/137 were discordant, kappa: 0.93) but as anticipated, the clin-PMR-AS was lower than the PMR-AS. On a scatterplot representing the PMR-AS (y) according to the clin-PMR-AS (x), a straight line y=1.12 x clin-PMR-AS + 0.26 represented their association, and with use it for CRP imputation. The mean +/- SD was very close between the PMR-AS, clin-PMR-AS, and CRP-imputed-PMR-AS, respectively. Using cut off 0-7-17-∞, we obtained a slightly higher concordance for the CRP-imputed-PMR-AS (kappa=0.95). This suggested that it was not really necessary to do an imputation to separate patient in groups of PMR-AS except for high clin-PMR-AS. The replication in the TENOR cohort before and after treatment by tocilizumab confirmed that CRP-imputed-PMR-AS did not modify the results using the original PMR-AS (during treatment by tocilizumab, means for PMR-AS, clinPMR-AS, and CRP-Imputed-PMR-AS were 11.3+/-.8.1, 11+/-.8.1 and 12.0+/-.9, respectively).

Conclusion: This study supplies evidence that a CRP-imputed-PMR-AS may be used to monitor PMR activity for patients without available CRP or treated by anti IL6. Nevertheless, use of PMR-AS (or Clin-PMR-AS) in patients treated by tocilizumab lead to a very small proportion of false classification of patient splited in low-disease activity or high-disease activity.

Oral presentation 976:
Efficacy and Safety of Tocilizumab in Patients with Refractory Takayasu Arteritis: Results from a Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial in Japan

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Background/Purpose: Glucocorticoids (GC) are the mainstay of treatment options for patients (pts) with Takayasu arteritis (TAK); however, long-term GC therapy is associated with adverse events (AEs). TAK pts have elevated IL-6 levels, which correlates with TAK disease activity (Rheumatology. 2006; 45:545-48). Tocilizumab (TCZ), a humanized anti–IL-6 receptor antibody, was investigated for the treatment of relapsing TAK.

Methods: Pts ≥12 y with TAK (Circ J. 2011; 75:474-503) receiving GC (≥0.2 mg/kg/d prednisolone equivalent) who had relapsed ≤12 weeks (wks) before enrolment were randomly assigned 1:1 to subcutaneous (SC) TCZ 162 mg or placebo (PBO) every wk (QW). Pts had to be receiving a stable GC dose at ≥2× dose at relapse and to be in remission for 1 wk before randomization. During the double-blind (DB) period, which lasted until relapse occurred in 19 pts, background GC were tapered by 10%/wk from wk 4, which is more rapid than in a general clinical setting. The primary end point was time to first relapse of TAK per protocol-defined criteria in the intent-to-treat (ITT) population estimated with the Kaplan-Meier analysis method and analyzed with the log-rank test stratified by age (<18 y, 18–64 y, ≥65 y). Time to relapse by Kerr’s definition (Ann Intern Med. 1994; 120:919-29) was a secondary end point.

Figure. Time to first relapse¹ (Kaplan-Meier analysis; ITT population

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*Defined as ≥2 of 5 signs of relapse present, including objective systemic symptoms, subjective systemic symptoms, elevated inflammation markers, vascular lesions, ischemic symptoms accompanied by organ lesions. Relapse was also considered to have occurred if there was severe aortic valve incompetence accompanied by symptoms of cardiac failure or if there were ischemic symptoms accompanied by organ lesions ≥grade 2 or ≥2 consecutive assessments.
**Results:** The ITT and safety populations included 18 TCZ pts and 18 PBO pts; median disease duration was 3.33 y and 2.89 y, respectively; mean ± SD GC dose at randomization was 0.57 ± 0.19 (TCZ) and 0.52 ± 0.16 (PBO) mg/kg/d; 38.9% of TCZ and 72.2% of PBO pts were HLA-B52 positive; 86.1% of pts were female. The per-protocol (PP) population included 16 TCZ and 17 PBO pts. No pts withdrew during the DB period. In the ITT population, 8 (44.4%) TCZ and 11 (61.1%) PBO pts relapsed. Estimated relapse-free rates at wk 24 were 50.6% and 22.9%, respectively, no statistical difference of time to first relapse between groups was seen (Figure; hazard ratio [HR], 0.41 [95.41% CI, 0.15-1.10]; p = 0.0596). Results were the same with Kerr’s definition. In the PP population, for relapse according to protocol-defined criteria, HR was 0.34 and p = 0.0345 (95.41% CI, 0.11-1.00), favouring TCZ. In addition, TCZ showed favourable trends in each sign of relapse, including objective systemic symptoms, subjective systemic symptoms, elevated inflammation markers, vascular lesions, and ischemic symptoms accompanied by organ lesions (ITT population). AEs were reported in 14 (77.8%) TCZ and 11 (61.1%) PBO pts, and serious AEs were reported in 1 pt and 2 pts. Infections were the most frequent AEs. No pts died.

**Conclusion:** There was a trend toward relapse suppression favoring TCZ, though the primary end point was not met. The safety of TCZ was consistent with the current safety profile for TCZ in RA/JIA. TCZ may be a promising treatment option for rapidly tapering GC in TAK pts.
Oral presentation 969:
Safety and Efficacy of Subcutaneous Tocilizumab in Early Systemic Sclerosis: Results from the Open-Label Period of a Phase 2 Randomized, Controlled Trial (faSScINATE Study)

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Background/Purpose: Systemic sclerosis (SSc) is a debilitating disease with few treatment options. Interleukin-6 (IL-6) appears to play a role in SSc pathogenesis (J Rheumatol 1998; 25:308; Pathobiology 1993; 61:239). Data from the 48-week, double-blind (DB), placebo (PBO)-controlled period of the faSScINATE trial of subcutaneous (SC) tocilizumab (TCZ) in patients with SSc have been published (Lancet 2016: doi: 10.1016/S0140-6736(16)00232-4). Herein we present data on the safety and efficacy of TCZ in SSc patients during 48 weeks of open-label (OL) TCZ treatment.

Methods: Patients ≥18 years of age with active SSc (≤5-year duration, modified Rodnan skin score [mRSS] 15-40, and elevated acute-phase reactants) diagnosed according to 1980 ACR criteria received OL TCZ 162 mg SC weekly from week 48 to week 96. Change from baseline in mRSS, patient-reported outcomes (PROs), and forced vital capacity (FVC) at week 96 were exploratory measures. Observed means used all available data.

Results: In total, 27 of 43 (63%) TCZ and 24 of 44 (55%) PBO patients completed week 96. Baseline (BL) characteristics were similar at BL and at entry into the OL period. Patients who switched from PBO→OL TCZ showed improvement in observed mean change from BL in mRSS at week 96 (–9.4) compared with the end of the 48-week DB period (–3.1). In patients initially randomly assigned to TCZ (TCZ→OL TCZ), mean change in mRSS was –5.6 at week 48 and –9.1 at week 96. In the OL period, improvements in PROs were noted at week 96 compared with week 48 in the PBO→OL TCZ group (mean [SD] change from BL at week 96 vs week 48 in HAQ-DI: –0.3 [0.4] vs 0.2 [0.4]; Patient Global VAS: –23.8 [36.0] vs –4.0 [24.0]; FACTIT-Fatigue: 11.3 [12.8] vs 1.4 [7.6]). Of patients who completed the study, none experienced a >10% decline in % predicted FVC during the OL period on TCZ therapy. Rates (95% CI) of serious adverse events/100 patient-years (PY) in the DB period were 76.1 (50.6, 110.0) in PBO patients and 66.7 (42.3, 100.1) in TCZ patients and were 36.0 (18.0, 64.4) in PBO→OL TCZ patients and 16.5 (5.4, 38.5) in TCZ→OL TCZ patients in the OL period. Rates (95% CI)/100PY of serious infections in the DB period were 10.9 (3.0, 27.9) in PBO patients and 34.8 (18.0, 60.8) in TCZ patients. In the OL period they were 19.6 (7.2, 42.7) in PBO→OL TCZ patients and 0.0 (0.0, 12.2) in TCZ→OL TCZ patients. No deaths occurred in the OL period (deaths in DB period: 3 TCZ, 1 PBO).

Conclusion: Although OL data have to be interpreted with caution, efficacy and safety in PBO treated patients who switched to OL TCZ were generally similar to those observed in patients randomly assigned to TCZ in the DB period. Results over 96 weeks of TCZ treatment suggest maintenance of the clinical response for mRSS in SSc patients. Rates of serious infection increased in PBO patients after they switched to OL TCZ. Long-term safety was consistent with the natural history of SSc and the safety profile of TCZ.
Poster 253: Corticosteroid-Free Tocilizumab Monotherapy for Adult Onset Still’s Disease: Results in Six Month

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Background/Purpose: To assess the efficacy and safety of tocilizumab (TCZ) monotherapy for the induction therapy of adult onset Still’s disease (AOSD) in a prospective, single-arm, single-center, cohort, pilot study.

Methods: Eight AOSD patients (male 2, female 6) who had agreed with our prospective trial since April 2010 till May 2015 were enrolled. Patients received 8 mg/kg of intravenous TCZ fortnightly for the first two months (five courses), then monthly for the next 5 months and after that TCZ was discontinued and patients were followed up for another 6 months with careful monitoring of clinical symptoms and signs related to AOSD relapses. In this report, we evaluated the efficacy and safety at the sixth month. Efficacy was evaluated by serum markers (WBC, CRP and serum ferritin), clinical symptoms and ratio of patients who required additional therapy, and safety was evaluated by adverse events for six months.

Results: The mean age was 45.2. Fever, arthralgia, rash and sore throat were observed in 100%(n=8/8), 100%(n=8/8), 87.5%(n=7/8) and 75.0%(n=6/8) respectively. LOCF analysis revealed that WBC, CRP and serum ferritin level decreased significantly from 14075 ± 4732/μl to 7042 ± 2939/μl, from 12.2 ± 7.4 mg/dl to 0.32 ± 0.62mg/dl and from 9176 ± 8077ng/ml to 3380 ± 5615ng/ml in 6 months respectively (each, P<0.01). The improvement rate of fever, arthralgia and eruption were 100%(n=8/8), 75.0%(n=6/8) and 71.4%(n=5/7). Only 2 patients required additional therapy (prednisolone). The reason of cessation consisted of lack of efficacy (25%, n=2) and adverse event (12.5%, n=1). An adverse event was UTI. There were no other significant adverse events.

Conclusion: TCZ monotherapy may be an alternative treatment strategy for AOSD.
Poster 1329:
Efficacy and Safety of Biologics in Relapsing Polychondritis: A National Multicenter Study in France

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Background/Purpose: No study has compared the efficacy and the safety of biologics in a large relapsing polychondritis (RP) cohort. This is the aim of the present study.

Methods: We conducted a national multicenter retrospective study in France including adult patients treated with biologics for RP from 2001 until July, 2015. Data were recorded at the time of biologic exposure (T0), at 3 and 6 months, and then every 6 months. Follow-up ended at biologic discontinuation or at the date of last available data. Efficacy outcomes were the intention-to-treat rates of partial (PR, defined by clinical improvement with persistent disease activity) or complete response (CR, defined by no clinical activity) during the first 6 months of exposure, and the evolution of the corticosteroid (CS) doses between T0 and month 6 for patients having a >6-month exposure to each biologic. Adverse drug reactions (ADRs) were described. We also compared the persistence of biologics (excluding rituximab) through Kaplan-Meier curves and the reasons for discontinuation. Factors associated to a PR or CR during the first 6 months of exposure to first-line biologics were investigated using a multivariate logistic regression model.

Results: The cohort included 41 patients. Mean age was 46.9 ± 12.5 years and 53.6% were females. Median time from RP diagnosis to first-line biologic T0 was 26.5 months. All patients satisfied to McAdam, Damiani and Michet diagnostic criteria. All but 2 patients had an active disease at first biologic prescription. Reasons for biologic initiation were CS dependency (n=28), CS resistance (n=11) or ADR to previous treatments (n=3). First-line biologics were TNF inhibitors (n=30), tocilizumab (n=5), rituximab (n=4), anakinra and abatacept (n=1 each). Twenty-eight patients were exposed to at least 2 lines of biologics (because of insufficient efficacy in14, relapses in 8 or adverse drug reactions in 9). In total, 105 biologic prescriptions were recorded (TNF inhibitors, n=60; tocilizumab, n=17; anakinra, n=15; rituximab, n=7; abatacept, n=6). Outcomes are presented in Table 1. PR or CR rate during the first 6 months was 62.9% while CR rate was 19.0%. There was only a modest reduction in the median CS dose. ADRs were mostly infections (n=42) and reaction at site of injection for subcutaneous biologics (n=12). Persistence was comparable among biologic classes (p=0.77). Among TNF inhibitors, the highest persistence was observed on adalimumab and the lowest for etanercept (log-rank test: p=0.02). In multivariate analysis, the single factor associated to PR or CR during the first 6 months of exposure to first-line biologic treatment was a history of chondro-sternal inflammation (OR: 5.75; 95% CI: 1.27-26.07; p=0.02) and there was a trend for nasal or auricular inflammation at biologic initiation (OR: 4.30; 95% CI: 0.93-19.78, p=0.09).

Conclusion: Overall, biologics are an interesting option for RP treatment.
Table 1. Efficacy and adverse drug reactions of biologics prescribed for relapsing polychondritis in 41 patients.

<table>
<thead>
<tr>
<th>Biologics</th>
<th>PR or CR at 6 months, n (%)</th>
<th>CR at 6 months, n (%)</th>
<th>Variation in CS dose at M6, mg PEQ, median (range)</th>
<th>Follow-up, months, median (range)</th>
<th>Discontinuation of biologic</th>
<th>Overall</th>
<th>Insufficient efficacy</th>
<th>Loss of efficacy</th>
<th>ADR</th>
<th>Stable CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=105)</td>
<td>66 (62.9%)</td>
<td>20 (19.0%)</td>
<td>-5.0 (-72.5; +70.0)</td>
<td>6.0 (0.1-80.8)</td>
<td>77 (73.3%)</td>
<td>36 (34.3%)</td>
<td>19 (18.1%)</td>
<td>22 (20.9%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TNF antagonists (n=60)</td>
<td>38 (63.3%)</td>
<td>14 (23.3%)</td>
<td>-5 (-53; +70)</td>
<td>6.0 (0.4-80.8)</td>
<td>47 (78.3%)</td>
<td>23 (38.3%)</td>
<td>15 (25.0%)</td>
<td>8 (13.3%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infliximab (n=20)</td>
<td>12 (60.0%)</td>
<td>7 (35.0%)</td>
<td>-5 (-50; +70)</td>
<td>6.5 (0.4-80.8)</td>
<td>16 (80.0%)</td>
<td>7 (35.0%)</td>
<td>6 (30.0%)</td>
<td>3 (15.0%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Adalimumab (n=25)</td>
<td>16 (64.0%)</td>
<td>5 (20.0%)</td>
<td>-7.5 (-53; +10)</td>
<td>8.0 (0.4-71.7)</td>
<td>18 (72.0%)</td>
<td>6 (24.0%)</td>
<td>7 (28.0%)</td>
<td>5 (20.0%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Etanercept (n=11)</td>
<td>8 (72.7%)</td>
<td>0</td>
<td>-5 (-50; +0)</td>
<td>5.5 (0.7-36.7)</td>
<td>11 (100%)</td>
<td>8 (72.7%)</td>
<td>2 (18.2%)</td>
<td>2 (18.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Golimumab (n=3)</td>
<td>2 (66.7%)</td>
<td>2 (66.7%)</td>
<td>-20</td>
<td>3.8 (3.4-7.2)</td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Certolizumab (n=1)</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>2.9</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>0</td>
<td>1 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab (n=17)</td>
<td>12 (70.6%)</td>
<td>2 (11.8%)</td>
<td>-1 (-72.5; +0)</td>
<td>3.7 (0.4-36.2)</td>
<td>10 (58.8%)</td>
<td>4 (23.5%)</td>
<td>2 (11.7%)</td>
<td>4 (23.5%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anakinra (n=15)</td>
<td>8 (53.3%)</td>
<td>2 (13.3%)</td>
<td>-12.5 (-20; +0)</td>
<td>2.6 (0.3-63.8)</td>
<td>13 (66.7%)</td>
<td>5 (33.3%)</td>
<td>0</td>
<td>7 (46.7%)</td>
<td>0</td>
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<tr>
<td>Rituximab (n=7)</td>
<td>5 (71.4%)</td>
<td>1 (14.3%)</td>
<td>-3 (-30; +5)</td>
<td>6.0 (42.8%)</td>
<td>3 (42.8%)</td>
<td>3 (42.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abatacept (n=6)</td>
<td>3 (50.0%)</td>
<td>1 (16.7%)</td>
<td>-16 (-40; +0)</td>
<td>9.5 (0.1-37.1)</td>
<td>6.0 (100%)</td>
<td>3 (50.0%)</td>
<td>2 (33.3%)</td>
<td>1 (16.7%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADR, adverse drug reaction; CR, complete response; PR, partial response.
Poster 1336:
Tocilizumab for Uveitic Cystoid Macular Edema Refractory to Other Synthetic and Biological Immunosuppressive Drugs. Multicenter Study of 25 Patients

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Background/Purpose: Our objective was to evaluate the efficacy and safety of Tocilizumab (TCZ) in a series of patients with refractory CME.

Methods: A Multicenter study of 25 patients with CME secondary to non-infectious uveitis who had inadequate response or intolerance to traditional treatment with corticosteroids and at least one conventional immunosuppressive drug including in most cases biological therapy. CME was defined by (OCT >300 μm). The outcome variables were the degree of inflammation of the anterior chamber and vitreous, visual acuity and macular thickness. Comparison of continuous variables was performed using the Wilcoxon test.

Results: 25 patients (17 females/8 males) with CME were studied. Mean age of 33.6±18.9 years. The associated disease was: juvenile idiopathic arthritis (n=9), Behçet’s disease (n=7), Birdshot retinochoroidopathy (n=4), idiopathic (n=4), sarcoidosis (n=1). The ocular pattern was: panuveitis (n=9), anterior uveitis (n=7), posterior uveitis (n=5), intermediate uveitis (n=4). Most patients had bilateral involvement (n=24). Prior to TCZ patients received: intraocular corticosteroids (n=22), iv. methylprednisolone (n=7), methotrexate (MTX) (n=19), cyclosporine A (CSA) (n=17), mycophenolate (n=4), azathioprine (n=2), cyclophosphamide (n=1), sulfasalazine (n=1), daclizumab (n=1), acetazolamide (n=1), thalidomide (n=1), leflunomide (n=2), infliximab (n=8), adalimumab (n=19), etanercept (n=2), golimumab (n=2), rituximab (n=2), abatacept (n=3), anakinra (n=1). TCZ administration schedule was 8 mg/kg/4 weeks iv. in all patients except in one that was administered every 2 weeks. TCZ was used in monotherapy (n=11) or combined with conventional immunosuppressive: MTX (n=6), CsA (n=5) and leflunomide (n=1). A statistically significant reduction was observed in macular thickness from 415.68±177.15 to 259.1±49.51 microns; (p=0.002) during the first year of treatment with TCZ. After a mean follow up of 12.7±8.34 months only minor side effects were observed: nausea (n=1), viral conjunctivitis and bullous impetigo (n=1). Remission was achieved in 14 patients. The prednisone dose was reduced from 15.9±13.6 at baseline to 3.1±2.3 after a year of treatment; p=0.002.

Conclusion: Treatment with TCZ seems an effective and safe treatment in patients with uveitic CME refractory to other synthetic and biological immunosuppressive drugs.
Poster 2954:
Anti-IL6-R Tocilizumab in Refractory Uveitis Associated with Behçet’s Disease. Multicenter Study of 11 Patients

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Background/Purpose: Treatment recommended in severe and/or refractory uveitis of Behçet disease is anti-TNFα therapy, usually infliximab (IFX) or adalimumab (ADA) (Levy-Clarke et al Ophthalmology 2014). However, in some cases these biologic agents are not effective, may be contraindicated or they are not well tolerated. IL-6 is a key cytokine in the pathogenesis of uveitis. Our aim was to evaluate the response to tocilizumab (TCZ) in uveitis associated with refractory Behçet disease.

Methods: Multicenter study of 11 patients with uveitis associated to Behçet disease. Patients had been treated with at least one conventional immunosuppressive drug and in most cases with anti-TNFα agents. The main parameters assessed were the visual acuity (VA) and the degree of intraocular inflammation. Cystoid Macular Edema (CME) was considered when OCT was greater than 300 μm.

Results: We studied 11 patients (7 men/4 women); mean age 38.45±20.42 years. Uveitis was bilateral (n=8); 7 of them with retinal vasculitis, 6 with CME and 1 with papillitis), anterior uveitis (n=2, also with severe arthritis) and posterior uveitis (1 case; also with retinal vasculitis and CME). The clinical course was chronic (n=4) or recurrent (7). Besides oral corticosteroids and before TCZ they had received: intraocular corticosteroids (n=10), i.v. methylprednisolone (10), methotrexate (MTX) (9), (cyclosporin A) CsA (8), azathioprine (AZA) (3), cyclophosphamide (2), mycophenolate (1) and colchicine (1). All of them had received other biologic drugs: Adalimumab (n=8), Infliximab (4), Golimumab (3), etanercept (1), canakinumab (1) and daclizumab (1). In 10 patients TCZ was prescribed at 8 mg/kg/i.v. monthly and in 1 patient 162 mg/week/sc. TCZ was given in monotherapy (n=7) and combined in 4 cases (2 MTX, 1 CsA, 1 AZA). After a mean follow up of 9.5±8.05 months, improvement was observed in the following items: a) Mean VA (0.38±0.32 to 0.73±0.35; p=0.002); b) Median cells in the anterior chamber (1 [0-2.5] to 0 [0-0]; p=0.005; c) Median vitritis (1 [0-2] to 0 [0-0]; p=0.003); d) retinal vasculitis (n=10 eyes [45.45%] with resolution in all cases e) Mean OCT (μ) (from 359.46±115.96 to 257.66±71.7, p=0.0009; f) 8 patients achieved complete remission, g) reduction in median dose of prednisone (30 [20-30] to 0 [0-5]; p=0.1). TCZ was withdrawn in 2 cases, due to an infusional reaction and 1 because of joint impairment.

Conclusion: Treatment with TCZ seems to be effective in patients with refractory uveitis due to Behçet’s disease.

### Table

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Conventional Immunosuppressive drugs before TCZ</th>
<th>Biologic drugs before TCZ</th>
<th>Immunosuppressive drugs combined with TCZ</th>
<th>Anterior chamber cells (onset/last visit)</th>
<th>Retinal Vasculitis (onset/last visit)</th>
<th>OCT (onset/last visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/27</td>
<td>MTX, CsA, CFM</td>
<td>MTX</td>
<td>0/0</td>
<td>Yes/No</td>
<td>296.5/243.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F/42</td>
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Abbreviations: M: Male; F: Female; MTX: Methotrexate; CsA: cyclosporin A; AZA: azathioprine; CYM: cyclophosphamide; MMF: mycophenolate; ADA: Adalimumab; IFX: Infliximab; GLM: Golimumab, ETN: Etanercept