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Vasculitis clinical and pathogenic highlights

OP0130 MEPOLIZUMAB FOR THE TREATMENT OF PATIENTS WITH EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS: A PHASE III RANDOMISED, PLACEBO-CONTROLLED TRIAL

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Background: Mepolizumab reduces blood eosinophils with concomitant clinical improvement in some hypereosinophilic syndromes and eosinophilic asthma.
Objectives: To investigate the efficacy and safety of mepolizumab in patients with eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss).
Methods: We conducted a Phase III, randomised, placebo-controlled, double-blind, parallel group, multi-centre study (NCT02020889) in patients with EGPA and a history of relapsing or refractory disease on stable therapy with prednisolone/prednisone ≥7.5–≤50mg/day with or without additional immunosuppressive therapy for ≥4 weeks. Patients were randomised 1:1 to receive mepolizumab 300mg or placebo subcutaneously, in addition to standard of care, every 4 weeks for 52 weeks. After Week 4, glucocorticoid dose could be tapered, per physician judgment, according to a suggested standard of care protocol. Co-primary endpoints (intent-to-treat [ITT] analysis) were accrued duration of remission (Birmingham Vasculitis Activity Score [BVAS]=0, prednisolone/prednisone dose ≤4mg/day) over 52 weeks; and the proportion of patients in remission at both Weeks 36 and 48. Secondary endpoints included average glucocorticoid dose during Weeks 49–52 and time to first EGPA relapse. Safety was also assessed.
Results: The ITT population included 136 randomised patients (mepolizumab n=68, placebo n=68). Baseline characteristics were similar between groups. Duration of remission accrued over 52 weeks was significantly prolonged with mepolizumab vs placebo (odds ratio: 5.91 [95% confidence interval [CI]: 2.68,13.03]; p<0.001); a significantly higher proportion of patients were in remission at Weeks 36 and 48 (32% vs 3%, odds ratio: 16.74 [95% CI: 3.61,77.56]; p<0.001). Significant reductions in average daily prednisolone/prednisone dose during Weeks 49–52 were seen with mepolizumab vs placebo (odds ratio: 0.20[95% CI: 0.09,0.41]; p<0.001). Median (range) prednisolone/prednisone dose during Weeks 49–52 was 5.0 (0.0–113.4)mg/day in the mepolizumab group and 10.0 (0.0–46.3)mg/day in the placebo group. Time to first EGPA relapse was significantly longer with mepolizumab vs placebo (hazard ratio: 0.32[95% CI: 0.21,0.50] ;p<0.001). Rates of adverse events (AEs) and serious AEs were similar for mepolizumab and placebo.
Conclusions: Treatment with mepolizumab significantly increased the likelihood and duration of remission, while reducing glucocorticoid use, in patients with EGPA, with a safety profile consistent with previous studies in severe asthma and EGPA. This demonstrates consistent and meaningful clinical benefits of mepolizumab in patients with EGPA.
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OP0131 OPTIMAL DOSE OF TOCILIZUMAB FOR THE TREATMENT OF GIANT CELL ARTERITIS: EFFICACY, SAFETY, AND EXPOSURE-EFFICACY ANALYSIS FROM GIACTA

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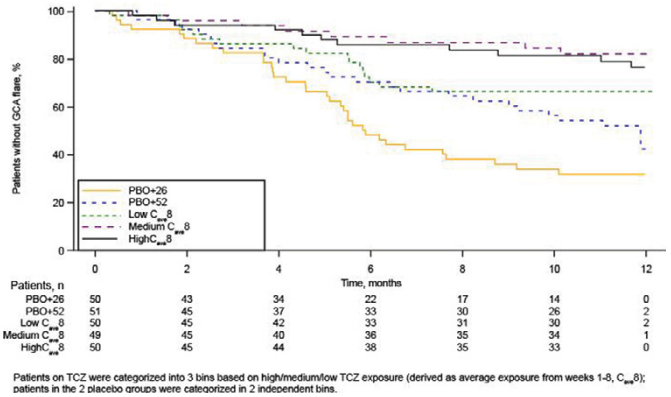
Background: GiACTA, a randomized, double-blind, placebo-controlled trial, evaluated the efficacy and safety of tocilizumab (TCZ), an IL-6 receptor-α inhibitor, in patients with giant cell arteritis (GCA).[1,2]
Objectives: Secondary analyses to evaluate the differential efficacy and safety of TCZ between patients with new-onset and relapsing GCA and to evaluate the TCZ exposure-efficacy relationship at week 52 of the trial.
Methods: Patients aged ≥50 years with active GCA were randomly assigned 1:1:2:1 to short-course prednisone (PBO+26), long-course prednisone (PBO+52) (26-week or 52-week prednisone taper + weekly subcutaneous [SC] placebo, respectively), weekly (TCZ-QW) or every-other-week (TCZ-Q2W) SC TCZ 162 mg + 26-week prednisone taper. Subgroup analysis was performed by disease-onset status (new-onset vs relapsing) to evaluate the proportions of patients in sustained remission at week 52 and time to flare. The impact of TCZ exposure, categorized into high, medium and low tertiles, on time to flare was evaluated across all patients in all treatment arms.
Results: Randomization included 251 patients, 119 (47%) with new-onset and 132 (53%) with relapsing GCA, distributed evenly across groups. Higher proportions of patients achieved sustained remission in the TCZ vs placebo groups regardless of disease onset (new-onset, relapsing–TCZ-QW: 59.6%, 52.8%; TCZ-Q2W: 57.7%, 47.8%; PBO+26: 21.7%, 7.4%; PBO+52: 21.7%, 14.3%, respectively). Patients with relapsing disease at baseline were in relapse-free remission longer and thus had lower risk for flare (hazard ratio) when treated with TCZ-QW than TCZ-Q2W. Hazard ratio (99% CI) for flare vs PBO+26 was 0.23 (0.09–0.61) for TCZ-QW and 0.42 (0.14–1.28) for TCZ-Q2W; vs PBO+52 it was 0.36 (0.13–1.00) for TCZ-QW and 0.67 (0.21–2.10) for TCZ-Q2W. TCZ exposure-efficacy analysis showed that most patients in the low exposure tertile had been treated with TCZ-Q2W (80%) whereas those with medium and high exposure primarily received TCZ-QW (84% and 98%, respectively). Kaplan-Meier analysis demonstrated that patients with higher exposure benefited from a longer time to flare (Figure). Adverse events (AEs) were similar across groups. Serious AEs were reported in 15.0% TCZ-QW, 14.3% TCZ-Q2W, 22.0% PBO+26 and 25.5% PBO+52 patients; rates were similar between new-onset and relapsing patients.

Figure. Time to first GCA flare after clinical remission by exposure (tertile of $C_{ave}8$)



Patients, n						
PBO+26	50	43	34	22	17	14	0
PBO+52	51	45	37	33	30	26	2
Low $C_{ave}8$	50	45	42	33	31	30	2
Medium $C_{ave}8$	49	45	40	36	35	34	1
High $C_{ave}8$	50	45	44	38	35	33	0

Patients on TCZ were categorized into 3 bins based on high/medium/low TCZ exposure (derived as average exposure from weeks 1-8, $C_{ave}8$); patients in the 2 placebo groups were categorized in 2 independent bins.

Conclusions: The compelling treatment effect of TCZ in GCA patients as measured by sustained remission to 52 weeks was consistent regardless of disease-onset status. Duration of relapse-free remission until flare was longer in patients with higher TCZ exposure, most notably in relapsing patients treated with TCZ-QW.
References:
[1] Unizony SH et al. Int J Rheumatol. 2013;2013:912562.
[2] Stone JH et al. 2016 ACR/ARHP Annual Mtg; Washington, DC; A911.
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OP0132 LOW-DOSE INTERLEUKIN-2 SELECTIVELY RESTORE REGULATORY T CELL NUMBERS IN PATIENTS WITH BEHCET'S DISEASE

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Background: The lack of $CD4^+CD25^+Foxp3^+$ T regulatory cell (Treg) has been associated with human systemic autoimmune diseases, such as Behcet's disease (BD). IL-2, an essential growth and survival factor for Treg cells.However, the significance of Treg cells in the pathogenesis and the effect of low dose of IL-2 on BD are remain to investigate.
Objectives: The lack of $CD4^+CD25^+Foxp3^+$ T regulatory cell (Treg) has been associated with human systemic autoimmune diseases, such as Behcet's disease (BD). IL-2, an essential growth and survival factor for Treg cells.However, the significance of Treg cells in the pathogenesis and the effect of low dose of IL-2 on BD are remain to investigate.
Methods: Eighty patients with BD and seventy healthy donors were enrolled. $CD4^+$T cell subsets in peripheral blood mononuclear cells from these people were measured by multicolour flow cytometry. Twenty-six patients were treated daily with subcutaneous injections of 0.5 million IU of human IL-2 for five consecutive days, $CD4^+$T cell subsets were analysed before and after treatment by flow cytometry.
Results: Compared to health control,the absolute counts of circulating Treg cells were significantanty decreased in patients with BD (median:29.93 cell/uL VS median:33.16 cell/uL; p=0.039) and it is negative correlation with disease activity. While the ratios of Th17/Treg in patients with BD (median:0.29;n=80,p=0.034) were significantly higher than those of health control (median:0.2;n=70).No diffrernce in the absolute counts of circulating Th17 cells ($CD4^+IL\text{-}17^+$) between patients with BD and health control. Treatment of patients with BD with a low-dose of IL-2 regimen selectively increased the absolute counts of Treg cells, from a median of 18.97cell/uL to 74.68 cell/uL (at 5 days) (p=0.000). No significant difference was observed in the absolute counts of circulating Th17, Th1 and Th2 cells after IL-2 treatment.
Conclusions: Th17/Treg cells may play a role in the pathogenesis of Patients with BD, low-dose of IL-2 proposes a selective biological treatment strategy by restoring immune tolerance.
Disclosure of Interest: None declared
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OP0133 COLOUR DOPPLER ULTRASONOGRAPHY OF FACIAL AND OCCIPITAL ARTERIES IN PATIENTS WITH GIANT CELL ARTERITIS: THE FREQUENCY OF INVOLVEMENT AND THE ROLE OF THEIR ASSESSMENT IN DAILY PRACTICE: A PROSPECTIVE STUDY

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Background: Giant cell arteritis (GCA) is the most common systemic large and medium size artery vasculitis in Western countries. Colour Doppler Sonography (CDS) allows us to study the involvement of the cranial arteries other than the temporal arteries in GCA which cannot be safely biopsied such as the facial (FaA), and occipital (OcA) arteries.
Objectives: We aimed to estimate the frequency of the FaA, and OcA involvement in GCA; and to explore the clinical characteristics of these subgroups of patients.
Methods: From 1 January 2014 to 31 December 2016, we prospectively performed a CDS of the FaA, and OcA in addition to the temporal (TA), and the extracranial supra-aortic arteries in all newly diagnosed patients suspected of having GCA. We used a Philips IU22 with a 5–17.5 MHz multi-frequency linear probe from January 2014 to August 2016 and a Philips Epiq 7 with a 5–18 MHz multi-frequency linear probe from September 2016 to December 2016. All the arteries were evaluated in two planes for the highly specific *halo*-sign.
Results: During the 36-month observation period we performed a CDS of the cranial and extra-cranial arteries in 93 GCA (66.7% female) patients. The patients' median (IQR) age was 73.7 (66.1–79.1) years, and they had a median (IQR) symptom duration of 30 (21–90) days. We observed the *halo*-sign on the FaA, and OcA in 38 (40.9%), and 29 (31.2%) cases, respectively. The FaA, and OcA were simultaneously affected in 18/93 (19.4%) cases. The FaA, or OcA were affected in 4/22 (18.2%) patients with a negative TA CDS. Patients with an FaA involvement had the highest frequency of severe visual manifestations, with permanent visual loss representing 70% of all visual manifestations. Patients with an OcA involvement least commonly had extracranial large vessel disease.
Conclusions: A fifth of patients with a negative CDS of the TAs had signs of vasculitis only on the CDS of the FaA, or OcA. The CDS of the FaA, and OcA identified approximately 5% more patients with GCA than the CDS of the TA alone.
Disclosure of Interest: None declared
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OP0134 LONG TERM OUTCOME AND PROGNOSIS FACTORS OF COMPLICATIONS IN TAKAYASU'S ARTERITIS: MULTICENTER STUDY OF 318 PATIENTS

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Objectives: To assess long term outcome and to elaborate a prognostic score for vascular complications in patients with Takayasu arteritis (TA).
Methods: Retrospective multicenter study of characteristics and outcome of 318 TA patients [86% of females; median age 36 [25–47] years; median follow-up of 6.1 years] fulfilling ACR and/or Ishikawa criteria. Factors associated with the event free survival (EFS), relapse free survival (RFS) and incidence of vascular complications were assessed. A prognostic score for vascular complications was elaborated based on a multivariate model.
Results: The 5- and 10-years event free survival (EFS), relapse free survival (RFS) and complication free survival were 48.2% (42.2;54.9) and 36.4% (30.3;43.9), 58.6% (52.7;65.1) and 47.7% (41.2;55.1), and 69.9% (64.3;76) and 53.7% (46.8;61.7), respectively. Progressive disease course (p=0.018) and carotidodynia (p=0.036) were independently associated with EFS. Male gender (p=0.048), elevated C reactive protein level (p=0.013), and carotidodynia (p=0.003) were associated with RFS. Progressive disease course (p=0.017), thoracic aorta involvement (p=0.009), and retinopathy (p=0.002) were associated with complication free survival. We define high risk patients for vascular complications according to the presence of two of the following factors (i.e a progressive clinical course, thoracic aorta involvement and/or retinopathy). The probability of complication free survival at five years was 78.4% (69.4;88.6) and 51.5% (38.3;69.2) in the low risk and high risk group, respectively.
Conclusions: This nationwide study shows that 50% of TA patients will relapse and experience a vascular complication at 10 years. We could define high risk TA patients for vascular complications.
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OP0135 TOCILIZUMAB IN GIANT CELL ARTERITIS: GIACTA TRIAL VERSUS A SERIES OF PATIENTS FROM CLINICAL PRACTISE

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Background: Baseline characteristics of patients from GiACTA trial have been recently reported at the ACR-2016 conference (1). GiACTA trial is a randomized, phase III controlled clinical trial evaluating the efficacy of tocilizumab (TCZ) in giant cell arteritis (GCA) (2). We had previously published a multicenter study on the use of TCZ in refractory GCA in a clinical practice setting (3).
Objectives: Our aim was to compare both studies, emphasizing on the baseline characteristics of the patients.
Methods: Comparative study between the GiACTA trial and our multicenter clinical practice study. In the latter, the diagnosis of GCA was established by the ACR-1990 criteria and in the GiACTA trial by the ACR modified criteria. In the clinical practice study, TCZ was used at standard IV dose (8 mg/kg/month), while in the GiACTA trial it was given subcutaneously (162 mg every 1 or 2 weeks, depending on the therapeutic arm). Quantitative variables were expressed as mean ± SD and were compared with the Student's t-test. Dichotomous variables were expressed as percentages and compared using the chi-square test.
Results: In the GiACTA trial, 47.4% were newly diagnosed GCAs, while in the clinical practice study were all refractory to conventional treatment. The TABLE summarizes the main baseline characteristics of both studies. Compared with the GiACTA trial, in the clinical practice study were significantly greater: a) the mean time between the diagnosis of GCA and the onset of TCZ, b) the proportion of patients with polymyalgia rheumatica and ischemic optic neuritis, c) the proportion of positive PET/CT scans, d) the mean value of ESR, and e) the proportion of patients who had received conventional immunosuppressant agents (mainly MTX) before starting TCZ. There was also a significant lower proportion of sustained remission in the clinical practice study. When only GiACTA patients with