FRI0262

CLINICAL OUTCOMES OF PATIENTS WITH GIANT CELL ARTERITIS WITH POLYMYALGIA SYMPTOMS ONLY VS CRANIAL SYMPTOMS ONLY TREATED WITH TOCILIZUMAB OR PLACEBO IN THE GIACTA TRIAL

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Background: GiACTA, a randomized, double-blind, placebo (PBO)-controlled study, demonstrated the efficacy and safety of tocilizumab (TCZ) in patients with giant cell arteritis (GCA).¹ Growing evidence has shown that TCZ is also effective for the treatment of polymyalgia rheumatica (PMR); however, data on this are limited.^{2,3}

Objectives: To evaluate the efficacy of TCZ in patients with GCA presenting with cranial symptoms only or PMR symptoms only in GiACTA.

Methods: GiACTA randomized 251 GCA patients to receive weekly or every other week TCZ plus a 26-week prednisone taper (TCZ + prednisone) or PBO plus a 26- or 52-week prednisone taper (PBO + prednisone).¹ In this post hoc analysis, baseline characteristics, sustained remission rate, number of flares, annual flare rate, time to flare, cumulative prednisone dose and safety were assessed in patients with PMR symptoms only and patients with cranial symptoms only at diagnosis. Disease flare was defined as the recurrence of signs or symptoms of GCA (including PMR) or an elevation in erythrocyte sedimentation rate attributable to GCA.

Results: Of 146 patients included in the analysis, 52 had PMR symptoms only and 94 had cranial symptoms only at diagnosis. Demographics and other patient characteristics are shown in **Table 1**. The hazard ratios for flare in patients receiving TCZ vs PBO were 0.77 (95% CI, 0.26-2.32) for patients with PMR symptoms only and 0.37 (95% CI, 0.13-1.01) for patients with cranial symptoms only. Of patients with PMR symptoms only, 18 flares occurred in 13/31 patients (41.9%) in the TCZ group and 20 flares occurred in 12/21 patients (57.1%) in the PBO group. Of patients with cranial symptoms only, 19 flares occurred in 12/58 patients (20.7%) in the TCZ group and 25 flares occurred in 17/36 patients (47.2%) in the PBO group (**Table 2**). For both the PMR and cranial symptoms only groups, annual flare rates were lower in patients receiving TCZ compared with those receiving PBO. The occurrence of adverse events and serious adverse events was similar between groups (**Table 2**).

Conclusion: TCZ improved clinical outcomes in patients who presented with PMR symptoms only or cranial symptoms only at diagnosis as indicated by a reduced incidence of flares. These findings suggest that TCZ is effective in patients with GCA with PMR or cranial symptoms.

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Table 1. Patient Characteristics and Treatment at Study Baseline

	PMR Symptoms Only at Diagnosis (n = 52)	Cranial Symptoms Only at Diagnosis (n = 94)
Age, mean (SD), y	64.5 (8.3)	70.8 (7.8)
Female, n (%)	39 (75.0)	64 (68.1)
White, n (%)	51 (98.1)	91 (96.8)
Weight, mean (SD), kg	70.06 (14.09)	71.78 (16.10)
Body mass index, mean (SD), kg/m ²	24.81 (3.95)	26.36 (5.44)
GCA diagnosis, n (%)		
Newly diagnosed	27 (51.9)	41 (43.6)
Relapsing	25 (48.1)	53 (56.4)
Disease duration, mean (SD), days	327.04 (600.89)	239.05 (404.94)
ESR, mean (SD), mm/h	24.98 (20.21)	24.56 (19.92)
CRP, mean (SD), mg/L	6.51 (9.44)	7.73 (12.70)
Diagnosis, n (%) ^a		
Positive temporal artery biopsy	9/12 (75)	72/79 (91.1)
Positive imaging	44/52 (84.6)	31/94 (33.0)
Prednisone dose, n (%)		
≤ 30 mg/d	27 (51.9)	53 (56.4)
> 30 mg/d	25 (48.1)	41 (43.6)
Treatment group, n (%)		
TCZ [†]	31 (59.6)	58 (61.7)
Placebo [‡]	21 (40.4)	36 (38.3)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMR, polymyalgia rheumatica; TCZ, tocilizumab.

^a Of patients with available results.

[†] TCZ 162 mg weekly or every other week with a 26-week prednisone taper.

[‡] Placebo with a 26- or 52-week prednisone taper.

Table 2. Clinical and Safety Outcomes

	TCZ [†] (n = 52)	Placebo [‡] (n = 94)	TCZ [†] (n = 58)	Placebo [‡] (n = 36)
Patients with ≥ 1 flare, n (%)	13 (41.9)	12 (57.1)	12 (20.7)	17 (47.2)
Patients with PMR symptoms, n (%)	8/13 (61.5)	7/12 (58.3)	7/12 (58.3)	8/17 (47.1)
Patients with cranial symptoms, n (%)	10/13 (76.9)	6/12 (50.0)	10/12 (83.3)	10/17 (58.8)
No. of flares	18	20	19	25
Patients with PMR symptoms, n (%)	10/18 (55.6)	10/20 (50.0)	7/19 (36.8)	11/25 (44.0)
Patients with cranial symptoms, n (%)	12/18 (66.7)	8/20 (40.0)	15/19 (78.9)	11/25 (44.0)
Annual flare rate, mean (SD) ^b	0.44 (0.85)	0.95 (1.24)	0.40 (0.83)	0.89 (1.81)
Patients with flare following remission, n (%)	11 (35.5)	11 (52.4)	11 (19.0)	10 (44.4)
Cumulative prednisone dose, prednisone, mg	1862.0	3671.5	1842.0	2965.5
Patients with ≥ 1 AE, n (%) ^c	30 (96.8)	20 (95.2)	55 (94.8)	30 (100)
Patients with ≥ 1 SAE, n (%) ^d	5 (16.1)	3 (14.3)	10 (17.2)	12 (33.3)

AE, adverse event; SAE, serious adverse event; TCZ, tocilizumab.

^a TCZ 162 mg weekly or every other week with a 26-week prednisone taper.

^b Placebo with a 26-week or 52-week prednisone taper.

^c Adverse event rate is calculated as the number of flares between the first clinical assessment of GCA and the first clinical assessment prior to entry into Part 2, divided by the time period between the 2 days, multiplied by 365.25.

^d Multiple occurrences of AE are included. Denominators are all AE in SAEs.

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FRI0263

GRANULOMATOSIS WITH POLYANGIITIS, (GPA): CARDIOVASCULAR MORBIDITY AND MORTALITY IN A POPULATION-BASED COHORT. A DANISH REGISTER STUDY

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Background: In order to understand and ultimately prevent cardiovascular (CV) morbidity and mortality in systemic inflammatory disorders we studied the epidemiology of CV disease in ANCA associated Vasculitis (AAV). There is growing evidence that both premature and pronounced atherosclerosis is associated with ANCA associated vasculitis (AAV) ¹⁻³. However, the exact mechanisms for CV involvement are unknown and probably multiple.

Objectives: To investigate if CV related comorbidity and death were increased among Danish AAV patients registered with a diagnosis of granulomatosis with polyangiitis (GPA) in Denmark.

To investigate if there was a temporal relation between diagnosis of GPA and CV disease and death.

Methods: A population-based cohort study was performed using the Danish Civil Registration System, the Danish National Patient Registry (all in-patient and out-patient contacts are registered with ICD diagnosis since 1995) and the Danish Cause of Death Register. Patients registered twice or more with a diagnosis of GPA (ICD8: 446.29 and ICD10: M313) during 1995-2016 were included. Annual incidence rate (IR), point prevalence (PP) and standardized mortality rate (SMR) were calculated. The entire adult population in Denmark served as control population. CV morbidity was divided into heart failure (HF) (ICD-10 code I42, I50, J81 and I110) and myocardial infarction (MI) (ICD-10 code I21-25). Death caused by CV disease (ICD-10 code I1-999) was registered.

Results: We identified 1829 individuals with GPA. The median annual IR was 20.5/1,000,000 and PP was 277/1,000,000 in 2015. Overall SMR was 2.14.

Among patients with GPA 171 had a hospital diagnosis of MI. Compared to the control population, the hazard ratio (HR) of MI was 2.47 (95% CI 1.45-4.11) during the first 3 months after the GPA diagnosis. From 3 months to one year declining to 1.41 (95%CI 0.80-2.49) and after 10 years the HR was still slightly increased to 1.64 (95%CI 1.20-2.23). The risk of a diagnosis of HF was markedly increased with a HR at 7.22 (95% CI 4.55-11.46) during the first 3 months after a GPA diagnosis, after three months up to one year 2.94 (95%CI 1.87-4.69), and 2.07 (95% CI 1.54-2.78) after 10 years.

The total number of CV deaths in the GPA cohort was 307. During the first three months after a GPA diagnosis, the HR was increased to 9.51 (95%CI 7.12-12.70) declining to 2.51 (95% CI 1.77-3.58) after one year, but still increased to 1.56 (95% CI 1.23-1.98) after 10 years.

Conclusion: In a population-based study we found an overall increased SMR. The risk of CV comorbidity and of CV death among patients with a register diagnosis of GPA was increased.

There was a striking temporal relation between a high HR of CV morbidity and mortality during the first year after the diagnosis of GPA. Nevertheless, the HR of CV morbidity and mortality was albeit lower still increased after 10 years with a diagnosis of GPA.

The result indicates a strong association between systemic vascular inflammatory disease and CV involvement. At the time of diagnosis of GPA systemic inflammatory activity usually is present and the results point towards an association of inflammation with CV risk-factors probably including premature and pronounced atherosclerosis. The persistence of increased HR of CV involvement after 10 years indicates a permanent influence on the risk factors.

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ADVERSE EVENTS DUE TO HIGH DOSE GLUCOCORTICOIDS – LESSONS FROM ANCA-ASSOCIATED VASCULITIS AND OTHER INFLAMMATORY DISEASES

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Background: High dose glucocorticoids (GCs) are a component of induction remission and maintenance regimes in ANCA-associated vasculitis (AAV) and are used in other inflammatory disorders. The adverse event (AE) profile of GC is well known and in AAV is believed to link to early mortality risk from infection as well as long term organ/tissue damage. However, it is known GC AE reporting is incomplete and EULAR made specific recommendations for such reporting in clinical trials (Van der Goes 2010).

Objectives: This systematic literature review aimed to examine AE rates and outcomes related to high dose GC use in AAV and to quantify AE risk in terms of GC dose and duration.

Methods: A systematic literature review was performed of studies published between 1 Jan 2007 and 30 January 2018. Data on GC-related AEs (defined as any untoward medical occurrence) and serious AEs (defined in European Medicines Agency CPMP/ICH/377/95) which threaten life or function were extracted from identified trials. The initial AAV search demonstrated incomplete GC data collection compared to EULAR recommendations in most AAV studies so the search strategy was extended to include other inflammatory disorders in which similar GC regimes and doses are used namely systemic lupus erythematosus, glomerulonephritis, pemphigus and giant cell arteritis.

Results: Three hundred and eleven studies of these 5 conditions were identified in which GC-related AEs were published. 38 studies were selected for a detailed AE analysis on the basis of their inclusion of full description of GC regime, actual delivered GC dose and patient exposure. Of the 62,630 patients enrolled in the 38 studies, 35,587 were exposed to GCs. 21 studies reported serious AEs, while 17 studies reported AEs only. The most common serious AEs related to specific organ damage - particularly musculoskeletal, ocular and neuropsychiatric - but mortality and infection were also observed. The most common AEs were metabolic conditions, with diabetes related events comprising 72% of the metabolic AEs, and weight gain comprising 15%.

	Serious adverse events	Adverse events
Number of patients in studies reporting GC-related events	2340	9602
Events reported (n)/%	840/36%	2479/26%
Most common events%	Mortality 14%	Metabolic 50%
	Infection 7%	Musculoskeletal 16%
	Organ damage 49%	Ocular 14%
		Infections 12%

Correlation analysis demonstrated mean total GC dose was positively related to risk of death ($r = 0.51$) and infection ($r = 0.49$) while GC therapy duration was related to risk of infection ($r = 0.62$).

Conclusion: GC-related AE reporting in clinical studies of high dose GCs could be improved. Serious AEs including organ damage, infection and mortality were reported and both total GC dose and therapy duration are important risk factors mortality and infection. Metabolic and musculoskeletal events are a particular patient burden. New therapeutic options for AAV and other disorders should aim to reduce this AE profile.

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FRI0265

ANTI-IGE AND ANTI-IL5 THERAPY FOR EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss syndrome, is a rare type of anti-neutrophil cytoplasm antibody-associated vasculitis, associated with asthma, nasal polypsis and rhinosinusitis, in which eosinophils play a key role.

Eosinophil targeted therapies alone or associated to conventional treatment with corticosteroids and immunosuppressant drugs may be useful in patients with refractory disease or asthma difficult to treat.

Objectives: To describe the efficacy and safety of eosinophil targeted therapies in patients with relapsing or refractory EGPA

Methods: Retrospective study including all patients with EGPA included at the REVAS Registry, who were treated with omalizumab, mepolizumab or reslizumab. Complete response (CR) was defined as the absence of asthma and/or sinonasal exacerbations with a prednisone dosage of ≤ 7.5 mg/day, and partial response (PR) when the prednisone dosage was ≥ 7.5 mg/day. Statistical analysis was performed using SPSS 20 package.

Results: Seventeen patients (median age 49 years) received omalizumab ($n=9$) for a mean period of 53.4 (5-91) months, mepolizumab ($n=7$) for a mean period of 13.6 (5-16) months, or reslizumab ($n=1$) for a mean period of 7 months, for severe steroid-dependent asthma (94.1%) and/or sinonasal involvement (82.4%). ANCA were positive in 8 (47.1%) cases with MPO specificity in 7 cases. All patients were receiving corticosteroids with a mean dosage of 15 mg/day prior to eosinophil targeted therapies institution. Four (57.1%) patients treated with omalizumab achieved a CR, 1 a PR, and 2 had no improvement. The median dosage of prednisone 6 months after omalizumab initiation was 10 (2.5-10) mg/day and the median dosage after 12 months 5 (0-10) mg/day. The median number of exacerbations decreased from 4 over the 6 months previous to therapy startment to 2 in the following 12 months. Both patients refractory to omalizumab were treated with mepolizumab with CR at 6 months in 1 case. Treatment with mepolizumab was also started in 4 patients treated with omalizumab after a prolonged period of treatment (72.4 months), due to recurrence of asthma and/or sinusitis, and peripheral blood eosinophilia $>10\%$. Three (75%) patients achieved a CR, and 1 patient experienced a major vasculitis relapse needing immunosuppressant drugs. Six (85.7%) patients initially treated with mepolizumab achieved a complete remission after 6-12 months of treatment. One patient achieved a PR. The median dosage of prednisone 6 months after mepolizumab initiation was 5 (3.1-6.8) mg/day and the median dosage after 12 months 3.5 (0-5) mg/day. The median number of exacerbations decreased from 2.5 over the 6 months previous to therapy startment to 1 in the following 12 months. The patient treated with reslizumab achieved a CR at 6 months of therapy. All 3 drugs were safe and well tolerated.

Conclusion: The results of the present study suggest that eosinophil targeted therapies have a corticosteroid-sparing effect in EGPA patients with asthmatic and/or sinonasal manifestations, and that may be used sequentially in refractory cases. However, reducing the corticosteroid dosage may also increase the risk of severe EGPA flares. More data are needed to widely recommend this therapy in EGPA patients.