OP0061

A PROOF-OF-CONCEPT STUDY TO ASSESS THE EFFICACY OF TOCILIZUMAB MONOTHERAPY AFTER ULTRA-SHORT GLUCOCORTICOID ADMINISTRATION TO TREAT GIANT CELL ARTERITIS - THE GUSTO TRIAL

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Background: Two randomised controlled trials [1, 2] demonstrated a glucocorticoid (GC)-sparing effect of tocilizumab (TCZ) of at least 50%. Long-term GC treatment leads invariably to numerous side effects, particularly in elderly giant cell arteritis (GCA) patients.

Objectives: The GUSTO (GCA treatment with ultra-short GC and TCZ) trial was set up to evaluate the efficacy and safety of TCZ-monotherapy after ultra-short GC treatment in new-onset GCA.

Methods: Eighteen patients with newly diagnosed GCA were enrolled in this investigator-initiated, single-arm, single-center, open-label clinical trial with Simon's two stage design (NCT03745586). Patients received 500mg methylprednisolone intravenously for 3 consecutive days. Thereafter, GC treatment was discontinued and TCZ (8mg/kg body-weight) was administered intravenously, followed by weekly subcutaneous TCZ injections (162mg) from day 10 until week 52. The primary endpoint was defined as the proportion of patients who achieved remission within 31 days and showed no relapse at week 24; the secondary endpoint included the proportion of patients with complete relapse-free remission of disease at week 52. Remission was defined as disappearance of GCA symptoms, whereas partial remission included the presence of mild symptoms (defined as non-ischemic with NRS<5/10, reported as mild, not occurring on most days of the week). An interim analysis of the primary endpoint was performed after the first 12 patients reached the primary endpoint.

Results: At baseline there were 12/18 female patients, and the median age was 71 (range 64-78) years. Overall, 15/18 had cranial symptoms (10/18 had jaw claudication, 6/18 had visual symptoms), 10/18 suffered from polymyalgia rheumatica (PMR)-symptoms, 16/18 had positive cranial ultrasound, and 13/18 had positive histopathology.

At interim analysis, only 25% (3/12) of patients achieved remission within 31 days and stayed relapse-free up to week 24. Thus, the null hypothesis that the proportion of responders would be smaller than 40% ($p=0.92$) was not rejected. Of the 18 patients recruited at the time of interim analysis, 14 achieved remission within 24 weeks (mean duration 11.1 (95% CI 8.3-13.9) weeks) and 13 showed no relapses up to 52 weeks (72%, 95% CI 47-90%). Overall, 3/18 patients were non-responders (2/3 with persistent cranial symptoms including one new-onset of an anterior ischemic optic neuropathy (AION); 1/3 with persistent PMR symptoms) and started on rescue GC-treatment, and 2/18 discontinued the study due

to an adverse event (hepatopathy and diverticulitis, respectively; 1/2 after induction of remission).

Figure 1 demonstrates remission status over time.

Conclusion: After a 3-days pulse of methylprednisolone, ensuing TCZ monotherapy induced and maintained remission until week 52 in 13/18 patients. The data add an important piece of evidence regarding the potency of blocking the interleukin-6 pathway in GCA and suggest that a substantial reduction of concomitant GC treatment in TCZ-treated GCA patients is feasible.

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Disclosure of Interests: Lisa Christ Shareholder of: F. Hoffmann-La Roche, Grant/research support from: Gilead Sciences; F. Hoffmann-La Roche; Pfizer, Luca Seitz: None declared, Godehard Scholz: None declared, Adela-Cristina Sarbu: None declared, Jennifer Amsler: None declared, Lukas Bütikofer: None declared, Christoph Tappeiner: None declared, Florian Kollert Shareholder of: Roche, Consultant of: Yes (Actelion, BMS, Boehringer-Ingelheim, Pfizer), Grant/research support from: Yes (Gilead, Pfizer), Employee of: Yes, I am currently employed by Roche and previously by Novartis, Stephan Reichenbach: None declared, Peter Villiger Speakers bureau: Roche, MSD, Abbvie, Pfizer, Novartis, Grünenthal, Celgene, Sanofi, Chugai, Consultant of: Roche, MSD, Abbvie, Pfizer, Novartis, Celgene, Sanofi, Grant/research support from: Roche, MSD, Abbvie
DOI: 10.1136/annrheumdis-2021-eular.522

Vasculitis - II

OP0062

CYTOKINE PRODUCING B CELLS SKEW MACROPHAGES TOWARDS A PRO-INFLAMMATORY PHENOTYPE IN GIANT CELL ARTERITIS

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Background: Giant cell arteritis (GCA) is the most frequent form of systemic vasculitis affecting the temporal artery (TA) and the aorta. Macrophages and T cells are well recognized players in the pathogenesis of GCA while B cells are often not taken into account. Recently, changes in the circulating B cell compartment were documented in GCA and B cells were found to organize into tertiary lymphoid organs at the site of vascular inflammation (TA and aorta).^{1,2} The exact role of B cells in GCA is still unknown as no disease-specific antibodies have been defined. However, beside their role in humoral immunity, B cells can also produce various cytokines. In GCA, peripheral B cells of treated GCA patients, showed an enhanced capacity to produce pro-inflammatory cytokine Interleukin (IL)6³ which is nowadays an important target of treatment in GCA.⁴ We hypothesize that B cells help shape the inflammatory response in GCA by producing effector and regulatory cytokines.

Objectives: We aimed to assess the cytokine profile of circulating and lesional B cells in GCA and studied the effects on macrophage skewing.

Methods: To assess B cells with the capacity to produce cytokines, cryopreserved peripheral blood mononuclear cells of 11 untreated GCA patients and 15 age- and sex-matched healthy controls (HC) were cultured for 3 days in the presence of CpG-ODN 2006. During the last 5 hours phorbol myristate acetate and Calcium Ionophore were added. Thereafter, intracellular effector (IL6, TNFα, IFNγ, LTb) and regulatory B cell-related cytokines (IL10) were measured with flow cytometry. To assess potential skewing of macrophages by B cell products, THP-1 cells were differentiated into macrophages and stimulated for 24 hours with supernatant from stimulated B cells (n=6). Expression of IL23, IL6, IL1b, TNFα, MMP9 and YKL40 was assessed on mRNA level with qPCR. To assess local cytokine production, TA (n=11) and aorta tissue samples (n=10) of histologically-proven GCA patients were stained to detect CD20, IL6, TNFα, IFNγ, LTb, and IL10 expression. For comparison, 14 aorta tissues samples of patients with an atherosclerosis-related aortic aneurysm were included.

Results: *In vitro* stimulated B cells from untreated GCA patients showed an enhanced percentage of IL6+ B cells (median (IQR); 44 (41-52)) and of IL6+TNFα+ B cells (12 (8-24)) compared to stimulated B cells from HC (IL6+: 28 (23-39), IL6+TNFα+: 6 (4-24)). In addition, soluble factors, secreted by GCA derived and stimulated B cells, skewed macrophages towards a pro-inflammatory phenotype with enhanced expression of IL23, IL6, IL1b, and TNFα. Furthermore, these macrophages also showed higher expression of the tissue remodelling factor MMP9 and the pro-angiogenic factor YKL40. At the site of vascular inflammation, B cells were detected in the regions with clear TNFα, IL6, IFNγ, LTb and IL10 expression in both the TA and aorta of GCA patients.

Figure 1. Disease status of patients at each visit (Day 10 - week 52, n=18).

Conclusion: This study demonstrates that circulating B cells of patients with GCA have the capacity to express pro-inflammatory cytokines (IL6 and TNF α) which can influence other cellular players in GCA. Specifically, B cell secreted soluble factors were able to skew macrophages towards a pro-inflammatory phenotype. In addition, this study provides evidence for an active role of B cells in shaping the cytokine milieu at the site of inflammation thereby revealing the B cell as a new target of intervention in GCA.

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Disclosure of Interests: Jacoba Carolien Graver: None declared, William Februy: None declared, Dania Altulea: None declared, Annemieke Boots Consultant of: Grunenthal, Peter Heeringa: None declared, Wajid Abdulahad: None declared, Elisabeth Brouwer Speakers bureau: Roche, fees paid to UMCG, Maria Sandovici: None declared

DOI: 10.1136/annrheumdis-2021-eular.1984

OP0063

SINGLE CENTRE EXPERIENCE OF THE CLINICAL SPECTRUM, AETIOLOGIES AND MANAGEMENT OF NON-INFECTIOUS AORTITIS

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Background: Aortitis, a rare form of large vessel vasculitis, may occur in the context of a primary systemic vasculitis, as a part of systemic autoimmune disease or in isolation. The evidence and guidelines to diagnose, manage and monitor aortitis remain limited. However, PET CT and vascular MRI scans have facilitated our ability to make the diagnosis more readily. The optimal management strategy and complication rates remain uncertain.

Objectives: Our aim was to explore the clinical, laboratory and radiological features of aortitis. We sought to review the management and complications of this illness by collecting detailed information on the outcomes and treatments used, including disease modifying agents (DMARDs) and biologics.

Methods: Patients diagnosed with aortitis since 2006 that had been managed in a single tertiary centre were identified using the Rheumatology Assessment Database Innovation in Oxford (RHADIO). Their medical notes were retrospectively reviewed using a local electronic patient record system and the following information was obtained: demographics, underlying risk factors, imaging and laboratory results (including biopsy reports if available), management and outcome.

Results: We identified 155 patients who met the inclusion criteria. There was a female preponderance of 57.4% (n=89). At the time of diagnosis, the average age was 69 (range 30-92) and the mean symptomatology length prior to diagnosis was 12 months (range 0-120). The majority of patients (60.4%, n=94) had aortitis secondary to giant cell arteritis (GCA), isolated aortitis was identified in 29.7% (n=46) and IgG4-related disease aortitis was uncommon (2.6%, n=4). Those with cranial GCA-like symptoms were diagnosed on average 3.9 months before those who presented differently (10.1 months versus 14.0 months).

Common presentations comprised: systemic inflammatory response syndrome (49.0%, n=76), cranial GCA-like symptoms (26.5%, n=41) and unexplained weight loss (24.5%, n=38). Importantly, 18.7% (n=29) of patients presented with ischaemic symptoms that included angina, TIAs/strokes and claudication. Aortic dissection was the primary presentation for 6.5% (n=10) of patients.

At presentation, the mean CRP was 84mg/L (range 1-249) and the ESR was 72mm/hr (range 2-164). Most (73.5%, n=114) had diagnostic PET CT changes. For those patients with GCA, diagnostic ultrasound changes were seen in 27.7% (n=26).

Nearly all were treated with prednisolone (92.3%, n=143) and all but 8 (5.1%) received a DMARD at some point. Methotrexate was the most commonly used DMARD (93.9%, n=138), followed by leflunomide (22.3%, n=35) and azathioprine (19.1%, n=28). Cyclophosphamide was used in 23.8% of patients (n=38) and 15 patients (9.7%) received tocilizumab.

Around a third (34.1% n=53/155) had received at least two DMARDs during their treatment course. On average, patients required 3.46 drugs to manage

their aortitis. Those who relapsed (43.2%, n=67) were more likely to have GCA (65.7%, n=44).

Vascular sequelae were present in 37.4% (n=58). The most common complications were ischaemic in nature with stroke/TIA and claudication reported in 16.8% (n=26). Aortic aneurysms were recorded in 11.6% (n=18) of cases and 5.1% (n=8) developed dissections despite being on treatment for their aortitis. One patient developed renal infarcts and ischaemic bowel leading to intestinal failure because of florid vasculitis.

Conclusion: Aortitis has a varied presentation with systemic inflammatory response syndrome being the most common. Delayed diagnosis remains a problem and especially for those with non-GCA related aortitis, which is likely to contribute to the risk of subsequent vascular complications. Vascular events including dissection are common, many of which could be preventable, emphasising the importance of early diagnosis and good disease control.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.1546

OP0064

TOCILIZUMAB IN CRANIAL AND EXTRACRANIAL REFRACTORY GIANT CELL ARTERITIS: A MULTICENTER STUDY OF 312 CASES

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