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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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).