OP0241
SERIOUS INFECTION WITH TOCILIZUMAB COMPARED TO TNF-INHIBITORS AND OTHER BDMARDS IN RHEUMATOID ARTHRITIS PATIENTS: DOES LINE OF THERAPY MATTER?

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Background: In the real-world, tocilizumab is prescribed to a population of patients different from those prescribed TNF-inhibitors, often older with longer disease duration, worse functional status and more previous b- or tsDMARDs.
Objectives: The aim of this study was to evaluate if and how the risk of serious infection on tocilizumab and other bDMARDs differs when stratifying by line of therapy in a real-world population of rheumatoid arthritis patients.
Methods: We included patients registered in the BSRBR-RA treated with tocilizumab, etanercept, adalimumab, infliximab, certolizumab, abatacept or rituximab, including biosimilars. Primary outcome was the occurrence of a serious infection (defined as infection requiring hospitalisation, intravenous antibiotics or resulting in death). Primary covariate of interest was line of therapy (from first to fifth line of therapy). Every change to another b- or tsDMARD was considered a new line of therapy, but not a change between a bio-original and a biosimilar. Hazard ratios (HR) of serious infections were estimated using an inverse probability weighted Cox regression, based on a propensity score including baseline patient and disease characteristics, and adjusting for time in study (see Table). The reference group was etanercept, which included the highest number of patients. Treatment exposure was analysed without and with stratification by line of therapy.

Table.

	N	ETN	TCZ	ADA	IFX	CERT	RTX	ABA
N	33,916	10,655	2,632	7,839	4,430	1,616	5,556	1,188
Patient-years	19,129	4,342	14,504	8,135	2,726	12,009	1,686	
Infections	807	192	681	481	74	433	74	
Incidence per 100 patient-years (95%CI)	4.2 (3.9-4.5)	4.4 (3.8-5.1)	4.7 (4.4-5.1)	5.9 (5.4-6.6)	2.7 (2.2-3.4)	3.6 (3.3-4.0)	4.0 (3.2-5.1)	
Unadjusted HR (95%CI)	Ref.	1.0 (0.9-1.2)	1.1 (1.0-1.2)	1.4 (1.2-1.6)	0.6 (0.5-0.8)	0.9 (0.8-1.0)	0.9 (0.7-1.2)	
Adjusted HR* (95%CI)	Ref.	1.2 (1.0-1.5)	1.1 (1.0-1.3)	1.3 (1.1-1.6)	0.8 (0.6-1.0)	1.0 (0.8-1.1)	1.2 (0.8-1.7)	
All lines of therapy	33,916	Ref.	0.9 (0.5-1.5)	1.1 (1.0-1.3)	1.3 (1.1-1.6)	0.6 (0.5-0.9)	1.6 (1.2-2.2)	
1 st line	16,152	Ref.	1.4 (1.0-2.0)	1.1 (0.9-1.4)	1.1 (0.7-1.6)	0.9 (0.4-2.2)	1.0 (0.8-1.2)	
2 nd line	10,378	Ref.	1.4 (0.9-2.3)	1.3 (0.8-2.2)	0.9 (0.4-1.9)	0.9 (0.3-2.9)	1.5 (0.5-1.2)	
3 rd line	4,676	Ref.	1.0 (0.5-2.3)	1.3 (0.4-3.7)	1.4 (0.5-4.4)	0.2 (0.0-2.1)	1.0 (0.5-2.2)	
4 th line	1,947	Ref.	0.9 (0.2-3.5)	2.5 (0.5-12.4)	0.7 (0.1-7.1)	3.3 (0.6-18.4)	0.9 (0.2-3.5)	
5 th line	763	Ref.						

ABA, abatacept; ADA, adalimumab; CERT, certolizumab; ETN, etanercept; HR, hazard ratio; IFX, infliximab; RTX, rituximab; TCZ, tocilizumab*Adjusted using inverse probability weighting (with age, gender, concomitant steroids, concomitant DMARDs, comorbidities, seropositivity, smoking, disease duration, HAQ and DAS28 at baseline in the model) and time since study entry (categorised from 0 to 4, 0 starting just before or at the moment of entering study, 1 starting during the first year, 2 starting during the second year until 4 for the fourth year and more)

Results: A total of 33,916 treatment courses were included (Table) contributing to 62,532 years of follow-up. Compared to etanercept, participants starting abatacept, tocilizumab and rituximab were older, had more previous bDMARDs, longer disease duration and more comorbidities. The crude HR of serious infections were higher with infliximab and adalimumab, lower with certolizumab and rituximab, and not significantly different for abatacept and tocilizumab compared to etanercept. After adjustment, HR of serious infections were higher with tocilizumab, adalimumab and infliximab. However, when stratified by line of therapy, HR were no longer significantly different compared to etanercept for tocilizumab, adalimumab and infliximab for most lines of therapy.

Conclusion: Whilst initially there appears to be a difference in rates of serious infection between biologic therapies, line of therapy may be a confounding factor when comparing the risk of serious infections between bDMARDs.

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Systemic sclerosis, myositis - etiology, pathogenesis and animal models

OP0242
EFFECTS OF THE AUTOTAXIN INHIBITOR ZIRITAXESTAT ON SKIN AND LUNG FIBROSIS IN A MURINE GRAFT-VERSUS-HOST DISEASE MODEL OF SYSTEMIC SCLEROSIS

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Background: There is an unmet medical need for new drugs to treat systemic sclerosis (SSc). Autotaxin (ATX) is a widely expressed enzyme that regulates diverse cellular processes, including proliferation, differentiation and migration, and has been implicated in the pathogenesis of SSc. Targeting ATX is a promising new strategy for treating SSc. The autotaxin inhibitor ziritaxestat (GLPG1690) is a potential first-in-class disease-modifying drug for SSc that has been shown to improve skin score in the Phase 2a NOVESa (NCT03798366) trial in patients with SSc.

Objectives: To investigate the effects of ziritaxestat in a chronic graft-versus-host disease (cGVHD) murine model of SSc.

Methods: Effects of ziritaxestat (10 or 30mg/kg twice daily [bid]) on disease activity were assessed in a cGVHD murine model of SSc (allogeneic bone marrow transplantation [BMT] with B10.D2 donor and BALB/c recipient; syngeneic mice as controls). Ziritaxestat or nintedanib (60mg/kg once daily [qd]) as active comparator was administered 21 d after BMT and continued for 35 d. Effects of ziritaxestat were assessed by clinical monitoring, histologic assessment of skin and lungs (dermal thickness, Ashcroft scores and collagen-covered area), immunofluorescence staining with Trichrome and Sirius Red for myofibroblasts, and biochemical analysis of collagen content, as measured by hydroxyproline levels.

Results: Ziritaxestat 30mg/kg bid for 35 days significantly reduced the clinical cutaneous score in the murine cGVHD model by 57% ($p<0.05$) compared with vehicle, and to a similar extent when compared with nintedanib 60mg/kg (38%; $p<0.05$). Dermal accumulation of collagen and dermal thickness (Figure) were reduced with ziritaxestat 10 and 30mg/kg compared with vehicle. At 30mg/kg, ziritaxestat reversed the increase in the allogeneic model ($p<0.001$), returning dermal thickness to the levels in non-fibrotic control mice. Ziritaxestat also significantly reduced pulmonary fibrosis in the cGVHD model, with reductions in the fibrotic lung area (ziritaxestat 10 and 30mg/kg; $p<0.001$ for both) and Ashcroft scores (ziritaxestat 30mg/kg; $p<0.05$). Ziritaxestat was generally well tolerated.

Conclusion: Ziritaxestat improved the histological, biochemical and clinical symptom readouts of dermal and pulmonary fibrosis in a murine model, consistent with a broad and rapid disease-modifying effect in SSc.

Figure. Effect of ziritaxestat on dermal thickness in a murine cGVHD model of SSc

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OP0243

AN APPROACH COMBINING TRANSCRIPTOMIC AND TOPOGRAPHIC ANALYSIS REVEALS A POTENTIAL ROLE OF PROTEASOME AND AUTOPHAGY DEREGLATION IN THE PATHOPHYSIOLOGY OF DERMATOMYOSITIS

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Background: Dermatomyositis (DM) is a rare autoimmune muscle disease characterized by an atrophy and a type-I interferon signature in perifascicular fibers. We recently showed that muscle mitochondrial dysfunction is also a characteristic of this disease that participates to both decrease exercise capacity and maintenance of inflammation (1). Pathophysiological mechanisms underlying these characteristics are unknown.

Objectives: The objective of this study is to reveal the mechanisms underlying the modifications of perifascicular fibers during DM, taking advantage of a method combining transcriptomic and topographical information.

Methods: Fourteen patients with recent (<6 months) untreated myositis (DM: n=7, other myositis: n=7) who underwent a biopsy of the deltoid muscle for diagnostic purposes were included. Seven other patients with suspected but not confirmed neuromuscular pathology (normal creatine kinase level, electromyogram and deltoid biopsy) were also included (no myopathy: n=7). Under the control of optical microscopy, perifascicular fibers (about 400 fibers) and endofascicular fibers (about 400 fibers) were microdissected by laser. The transcriptome of endofascicular fibers and perifascicular fibers in all three groups of patients were then obtained by massive sequencing of total messenger RNA. The DAVID database (2) (<http://david.abcc.ncifcrf.gov>) were used to determine the deregulated molecular pathways in the perifascicular fibers during DM.

Results: 482 transcripts were differentially expressed in perifascicular fibers of patients with DM compared to perifascicular fibers of the 2 other groups (348 overexpressed and 134 underexpressed). The most overexpressed transcripts were involved in the type I interferon response while the most underexpressed transcripts were involved in mitochondria and in proteasome functioning. The study of the transcripts differentially expressed in perifascicular versus endofascicular fibers revealed that there is a physiological perifascicular signature: in patients without myopathy, 83 genes were overexpressed and 54 were underexpressed in perifascicular fibers compared to endofascicular fibers. This physiological perifascicular signature was abolished in patient with myositis (DM and other myositis). In the group of patients with DM (but not other myositis), a specific perifascicular signature (18 genes overexpressed and 10 genes underexpressed in perifascicular fibers compared to endofascicular fibers) was identified. The most deregulated transcripts in DM perifascicular fibers were involved in autophagy/mitophagy, mitochondria and proteasome pathways.

Conclusion: In the physiological state, perifascicular fibers are characterized by a different transcriptomic profile from endofascicular fibers. During DM, this physiological perifascicular signature is abolished and replaced by a transcriptomic signature that reveal a potential role of proteasome and autophagy deregulation in the pathophysiology of DM.

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OP0244

28 NEW AUTOANTIBODIES AGAINST GPCR, GROWTH FACTORS AND GROWTH FACTOR RECEPTORS ARE ASSOCIATED WITH DISEASE MANIFESTATIONS IN SYSTEMIC SCLEROSIS

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Background: The morbidity and mortality of systemic sclerosis (SSc) are largely determined by vascular and fibrotic pathologies. Levels of autoantibodies (ab) against G protein-coupled receptors (GPCR), growth factors (GF) and growth factor receptors (GFR) are altered in SSc compared to healthy controls (HC). Thus, higher angiotensin II receptor type 1 - (AT1R) and endothelin receptor type A - (ETAR) ab levels are associated with severe disease and SSc-related mortality². CXCR3 and CXCR4 have predictive value for deterioration of pulmonary fibrosis (PF)³.

Objectives: We used statistical methods to identify associations between disease manifestations and 28 new ab directed against GPCR, GF and GFR in SSc.

Methods: Ab against the following targets were measured in sera from SSc patients (n = 177) and HC (n = 88): Adrenoreceptors alpha-1 (ADRA1), alpha-2 (ADRA2), beta-1 (ADRB1), beta-2 (ADRB2); muscarinoreceptors 1-5 (M1R - M5R); AT1R, ETAR, endothelin B receptor (ETBR); CXCR3, CXCR4; complement receptors 3a (C3aR) and 5a (C5aR); protease-activated receptors 1 (PAR1) and 2 (PAR2); vascular endothelial growth factor A (VEGFA) and its receptors 1 (VEGFR1) and 2 (VEGFR2), epithelial growth factor (EGF) - receptor (EGFR); hepatocyte growth factor (HGF) - receptor (HGFR), platelet-derived growth factor-AA (PDGFAA), placental growth factor (PIGF).

The organ involvement (PF, cardiac involvement, PAH, gastrointestinal tract) and quantitative markers (modified Rodnan skin score, SSc activity score, pulmonary function, cardiac enzymes and echocardiography, routine laboratory, autoimmune diagnostics) as well as demographic data were recorded retrospectively at the time of sample collection. Statistical analysis was performed using the Mann-Whitney U test (MWU), Pearson correlations, ROC analysis, and age-adjusted logistic regression models.

Results: In SSc 20 of 28 measured ab levels are significantly altered compared to HC. According to the Pearson correlation matrix, the ab-levels are highly correlated and build a network that differs between HC and SSc. Furthermore, altered network signatures are formed in the differentiated analysis of several disease manifestations of SSc such as SSc-subtype or PF. Based on ROC analysis, FGF-ab, ADRB1-ab and PIGF-ab are well suited to predict SSc (Figure 1).

In addition, limited cutaneous SSc (lSSc) patients displayed lower levels of most ab than diffuse cutaneous SSc patients, whereas cardiac and pulmonary involvement are associated with higher ab levels. In the logistic regression lSSc is associated with lower levels of ab against M1R, M2R, C5aR, ETAR, AT1R, PAR1, EGFR. Higher levels for ab against M1R, M2R, ETBR, C5aR are associated with PF, higher levels of ab against complement receptors, adrenoreceptors and EGF with NT-proBNP elevation.

Figure 1: Receiver operating characteristic analyses for 28 new autoantibodies in systemic sclerosis (n=177) compared with healthy controls (n=88). Ab against FGF, ADRB1 and PIGF may predict SSc.