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)								
All lines of therapy	33,916	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)
1 st line	16,152	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)	-
2 nd line	10,378	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)	0.9 (0.5-1.9)
3 rd line	4,676	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)	0.8 (0.5-1.2)	1.5 (0.7-2.9)
4 th line	1,947	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)	0.9 (0.4-2.3)
5 th line	763	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)	0.8 (3.5)

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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