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The Impact of Biologic DMARD Treatment on Sepsis and Mortality after Serious Infection

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Background/Purpose: Tumor-necrosis-factor-α inhibition (TNFi) was assumed to be a relevant mechanism for the treatment of sepsis[1]. However, randomized controlled trials failed to show a survival benefit caused by TNFi in patients with diagnosed sepsis[2].

Methods: We investigated the outcomes of serious infection (SI, N=1,170) reported in 947 patients in the German biologics register RABBIT (**R**heumatoid **a**rthritis: o**b**servation of **bi**ologic **t**herapy) as: (i) no complication of SI, (ii) sepsis following SI (≤30d), and (iii) death after SI (≤90d). We applied a GEE model for multinomial responses in longitudinal data [3] to evaluate the risks of sepsis and death (accounting for age at SI, sex, physical function, comorbid heart failure or renal disease, glucocorticoid (GC) dose and the disease-modifying anti-rheumatic drug (DMARD)). Biologic (b)DMARDs were grouped as TNFi or other classes of bDMARDs. Sensitivity analyses were applied: [a] in a subset of patients with pneumonia (N=298), [b] by restricting the conventional synthetic (cs)DMARD group to biologic naive patients and [c] by incorporating patients with incomplete data.

Results: 135 of 947 patients with an SI developed sepsis 137 times, 85 of 135 patients died due to sepsis. 53 patients died without known sepsis within 90 days after SI. The adjusted risk (odds ratio (OR)) of sepsis was significantly higher in older patients and in patients with chronic renal disease (Table). Patients with an SI who were exposed to bDMARDs and those with better physical function had a significantly lower risk to develop sepsis (Table). Risk factors of death after SI were higher age, glucocorticoids in high doses and heart failure, patients treated with bDMARDs and

those with better physical function had a significantly lower risk of death after SI. Results remained consistent in sensitivity analyses [a-c].

Table: Results of multinomial regression. Adjusted odds ratios (OR) show increase or decrease of the risks of sepsis or death. Reference group: patients with SI but no further complication.

	Sepsis		Death	
	OR	95% CI	OR	95% CI
Age (by 10 years)	1.41	[1.15; 1.74]	2.47	[1.61; 3.79]
Sex (male vs female)	0.99	[0.63; 1.55]	1.45	[0.74; 2.83]
% of physical function (10% improvement)	0.92	[0.84; 1.00]	0.86	[0.76; 0.98]
Glucocorticoids (<5 mg/d=Referenz)				
Glucocorticoids (5- <10 mg/d vs. Ref.)	1.26	[0.82; 1.93]	0.93	[0.47; 1.83]
Glucocorticoids (≥10 mg/d vs. Ref.)	1.66	[0.96; 2.88]	2.40	[1.04; 5.55]
csDMARDs (reference)				
TNFi	0.64	[0.42; 0.97]	0.48	[0.24; 0.95]
Other bDMARDs	0.45	[0.25; 0.80]	0.16	[0.05; 0.54]
Heart failure (yes vs. no)	1.38	[0.74; 2.56]	3.56	[1.73; 7.33]
Chronic renal disease (yes vs. no)	1.93	[1.19; 3.14]	1.51	[0.72; 3.17]

Conclusion: Our results suggest a protective effect of bDMARDs in terms of lowering the risk of sepsis after SI if patients were already exposed to bDMARDs at the SI. Further investigation is needed for each class of bDMARDs and separately for bacterial and viral SI.

[1] Waage A, et al. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. The Lancet 1987.

[2] Remick DG. Cytokine therapeutics for the treatment of sepsis: why has nothing worked? Current parmaceutical design 2003.

[3] Touloumis A, et al. GEE for Multinomial Responses Using a Local Odds Ratios Parameterization. Biom 2013.

Disclosure: A. Richter, None; **A. Strangfeld**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, Sanofi-Aventis, 9; **P. D. M. Schneider**, Abbvie, Actelion, Merck Serono, Pfizer, Roche, 2,Abbvie, Roche, UCB, 5,Abbvie, Chugai, Roche, Pfizer, UCB, 8; **T. Klopsch**, None; **A. Kapelle**, MSD, UCB, Chugai Roche,, 5,Abbvie, Chugai, Roche, MSD, Pfizer, UCB,, 2,Amgen, Pfizer, Abbvie, Chugai, Roche., 9; **J. Kaufmann**, None; **A. Zink**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, UCB., 9; **J. Listing**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,Pfizer Inc, 5.

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