Discontinuation of biologic DMARDs increases the risk of sepsis and mortality after serious infection

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Background: Three decades ago experimental studies suggested that TNF has a key role in the biological cascade of sepsis [1]. Nevertheless, randomized clinical trials failed to show that TNF inhibition (TNFi) is beneficial for the survival of patients with sepsis.

Objective: To investigate the impact of biological (b)DMARDs regarding the prevention of sepsis and mortality after serious infections (SI) in patients with rheumatoid arthritis.

Methods: We used data from patients with serious infections (N=859) of the German biologics register RABBIT (**R**heumatoid **a**rthritis: o**b**servation of **bi**ologic **t**herapy). The outcomes of SI: (i) no complication of SI, (ii) sepsis following SI (≤30d), and (iii) death after SI without sepsis (≤90d) were investigated as competing risks. We applied multinomial regression to evaluate the risks of sepsis and death simultaneously (accounting for age, sex, physical function, comorbid heart failure or renal disease, glucocorticoids and DMARD). Biologics were grouped into TNFi (adalimumab, etanercept, infliximab, golimumab, certolizumab) and other bDMARDs (abatacept, rituximab, tocilizumab). Sensitivity analyses were applied in a subset of patients with pneumonia (N=298) and by restricting the conventional synthetic (cs)DMARD group to biologic naive patients. Generalizability of results was tested by application of resampling techniques.

Results: Sepsis was reported in 135 patients, 53 patients died within 90d after SI without sepsis. At the time of SI, patients treated with bDMARDs were 3.8 years younger ($p<0.01$) and had fewer cases of chronic renal disease (12% vs. 16%, $p>0.13$) than patients on csDMARD treatment. There were no differences between DMARD groups in disease duration, DAS28, physical function or frequencies of heart failure ($p>0.42$). The crude odds ratio (OR) of developing sepsis (bDMARD exposed vs. bDMARD naive) was 0.6 (CI: 0.3; 0.9). However, 2 out of 3 patients (63%) treated with csDMARDs at SI had discontinued bDMARDs prior to SI. Their risk of developing sepsis was 2-fold increased (OR: 2.0, CI: 1.3; 3.0) compared to continuous bDMARD exposure.
The adjusted risk (odds ratio) of developing sepsis increased with age and was higher in patients with chronic renal disease. The risk was significantly lower when patients were exposed to bDMARDs at SI and in patients with better physical function (Table). Risk factors of death after SI were higher age, use of high GC dose and heart failure. The treatment with bDMARDs and better physical function had significant protective effects regarding mortality. Results remained consistent in sensitivity analyses.

	Sepsis after SI		Death after SI	
	OR	95% CI	OR	95% CI
Age at SI (by 10 years)	1.44	1.17; 1.77	2.52	1.68; 3.78
Sex (males vs. females)	1.00	0.64; 1.57	1.48	0.76; 2.87
Physical function (by 10% improvement)	0.91	0.84; 0.99	0.86	0.76; 0.97
GC (0-5 mg/d=Reference)				
GC (5-10mg/d vs. Ref.)	1.31	0.84; 2.03	1.00	0.49; 2.04
GC (>10mg/d vs. Ref.)	1.66	0.93; 2.96	2.34	1.00; 5.46
TNFi (yes vs. no)	0.55	0.36; 0.83	0.37	0.19; 0.74
Other bDMARD (yes vs. no)	0.42	0.23; 0.76	0.14	0.04; 0.48
Heart failure (yes vs. no)	1.59	0.86; 2.93	4.22	2.01; 8.87
Hypertension (yes vs. no)	0.92	0.60; 1.42	0.68	0.34; 1.37
Chronic renal disease (yes vs. no)	1.92	1.15; 3.20	1.63	0.76; 3.50

Table: Multinomial regression for the risk of sepsis and death after SI.

Conclusions: Results suggest that bDMARDs are capable to interfere with the biological pathway from SI to sepsis in a protective manner as already shown by Tracey et al. [1]. The impact of bDMARD discontinuation on the risk of sepsis should be taken into account in treatment decisions. Further investigation is needed to validate these results separately for bacterial and viral SI as well as for each individual bDMARDs.

References:

[1] Tracey KJ, Fong Y, Hesse DG et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. Nature 1987; 330:662-664