[2010] [OP0019] INCREASED RISK OF SEPSIS AFTER TERMINATION OF ANTI-TNF TREATMENT

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Background: Sepsis is an event associated with a lethality rate of up to 60%. Given the fact that an increased risk of bacterial infections has been consistently seen in patients treated with immunosuppressive drugs it is of interest to identify the magnitude of the risk and potential risk factors of septic complications in these patients.
Methods: Data from the German biologics register RABBIT, an ongoing prospective cohort study, were used to investigate the risk for developing a sepsis. We applied Cox proportional hazard regression to estimate the contribution of different risk factors on the development of a sepsis (during treatment and after discontinuation) and adjusted with inverse probability weighting for confounding by indication.
Results: The crude rates of septic events were lowest in biologic-naïve patients treated with conventional DMARDs only. The highest rates of septic events were found in patients who had been treated with biologic agents but had stopped treatment and were on treatment with DMARDs and/or glucocorticoids (GC) only (Table 1).

Table 1. Crude rates of sepsis per 1,000 patient years (p-yrs)

Treatment	n	p-yrs	Sepsis	Rate	Deceased
Anti-TNFα	3,792	9,822	29	3.0	11
Rituximab	858	721	5	6.9	4
DMARDs, previous biologics	1,014	2,269	29	12.8	27
DMARDs, biologic-naïve	1,735	5,067	13	2.6	6

In the multivariate Cox regression analysis, we found a significantly increased risk of sepsis in patients of higher age (Hazard ratio (HR) per 10 years increase: 1.6 [95%CI: 1.2–2.1]), with comorbid conditions (HR=1.3 [1.1–1.4] per co-morbidity), and treatment with GC (HR=1.3 [1.1-1.6] per 5 mg/d increase in dose). An improvement in the DAS28 reduced the risk (HR=0.94 [0.89–0.99] per 10% improvement). No significant associations were found for gender, MTX, leflunomide, other DMARDs, TNFα inhibitors, or anakinra. However, the time period following treatment termination with TNFα inhibitors was associated with a significantly ($p<0.0001$) increased risk of developing a sepsis. After adjustment for age, number of comorbid conditions, treatment with GC, and disease activity the HR of developing a sepsis within the first 6 months after treatment discontinuation was 7.1 [3.5–14.5]. There was no difference in risk between the first three months after treatment termination and month 4 to 6. In half of the patients (9/18), who developed a sepsis within the first 6 months after anti-TNFα discontinuation, treatment had been stopped because of a serious infection. In 4/18 (22%) patients the treatment had been stopped due to elective surgery.
In patients on rituximab treatment, we observed a significantly elevated risk for sepsis, if a 9 months risk window was applied (HR= 6.8 [1.8–26.3]). However, in 3 of the 5 patients who developed a sepsis under rituximab the previous anti-TNFα therapy had been stopped less than 4 weeks before the start of rituximab and the sepsis developed within the first 6 months after anti-TNFα treatment termination.

Conclusion: Our data suggest that the time period following anti-TNFα treatment termination is associated with a highly elevated risk of developing a sepsis. This implies that patients should be monitored carefully, when anti-TNFα treatment had to be stopped because of an infectious episode.
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