Does the risk of serious infections in anti-TNF treated patients decrease over time?

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Purpose: Data of the German biologics register RABBIT were used to determine the influence of anti-TNF treatment, outcome of this treatment, confounding by indication, and dropout processes on the risk of developing serious infections. Our objective was to investigate whether there is a decline in the risk of serious infections in patients with rheumatoid arthritis (RA) receiving TNFα inhibitors and if so what are the reasons for.

Methods: RABBIT is an ongoing prospective cohort study. Patients are enrolled in the biologics groups at start of an approved biological therapy or at start of a new DMARD treatment after at least one DMARD failure. At fixed time points at follow-up rheumatologists assess the clinical status, report treatment details and adverse events according to ICH guidelines.

Results: Data of 5,044 RA patients was available for the analysis. Among them 3,270 received TNFα inhibitors and 1,774 DMARDs at study entry. Crude rates of serious infections increased slightly in DMARD treated patients from 2.4 /100 patient years (PY) in the 1st year to 2.5, 2.8/100 PY in the 2nd and 3rd year respectively (p=0.74) whereas in anti-TNF treated patients a significant decrease (p<0.0001) from 5.0/100 (PY) in the 1st year to 3.1/100 PY in the 2nd and to 2.0/ 100 PY in the 3rd year was observed. Already in the first year there were highly significant differences in the crude infection rates of anti-TNF treated patients who completed treatment for at least 12 months (1.8/100 PY), switched to treatment with DMARDs (10.2/100PY) dropped out or switched to non-anti-TNF biologics (16.8/100 PY). This selection process led to a lower exposure time under anti-TNF treatment in the 2nd (56% of time) or 3rd year (68% of time) in patients with vs. those without serious infections in the 1st year who were to more than 85% of the time in the following years exposed to anti-TNF agents. This process caused a depletion of susceptibles since patients with one serious infection in the first year were at a significantly higher risk of developing a serious infection in the following years. By applying marginal structural models to account for time-varying risk factors and selection processes at follow-up (confounding by indication, dropouts) we could explain the decrease in the relative risk (RR) of serious infections under anti-TNF treatment compared to DMARD in the second year (crude RR: 1.3, adjusted RR: 2.0 (95% CI: 0.8 – 4.9). According to these models the decrease was mainly caused by confounding by indication at follow-up. For the 3rd year simple comparisons suggest similar selection processes. It remains, however, unclear whether the multivariate models are robust enough to adjust for all confounding factors till the end of the 3rd year.

Conclusion: Patients with serious infections were at higher risk of further infections and were less likely treated with anti-TNF agents at follow-up. Our data suggest that the depletion of susceptibles is a main cause for the observed decrease in the serious infection rates of anti-TNF treated patients.