Reactivation of herpesviruses (HHV-1 and HHV-3) infections is increased in RA patients treated with adalimumab or infliximab

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Background: There is likely an increased risk of bacterial infections in patients treated with TNFα inhibitors (Strangfeld A, Listing J 2006). Less is known, however, with regard to the viral infection risk of these agents.

Objectives: To estimate the hazard risk of (recurrent) herpes infections in patients with rheumatoid arthritis (RA) who are treated with a biologic agent compared to patients receiving conventional DMARDs.

Methods: Data of RA patients enrolled into the German biologics register RABBIT between May 2001(start of RABBIT) and June 2006 were used for the analysis. Treatment, clinical status and adverse events were assessed at fixed time points of follow up. Time to the first (re-)occurrence of a herpes infection (herpes simplex or herpes zoster) was investigated by means of Cox proportional hazard regression with time-depending co-variates. At each point in time a patient was considered as being exposed to adalimumab, etanercept, infliximab or conventional DMARDs only if she/he received such a treatment within the last 3 months (3-months risk window approach).

Results: Among the 4,393 patients included in the analysis, n=1,132 received etanercept (ETA), n=563 infliximab (INF), and n=1,155 adalimumab (ADA). N=1,543 patients were enrolled in the control group.

In total 102 herpes infections were reported: 64 cases of herpes zoster (among them 13 multi-dermatomal, 2 ophthalmic zoster), 37 cases of herpes simplex, and one patient with herpes oesophagitis. Only 13 of all herpes infections were considered as serious, five of them in patients of the control group.

With a Cox regression we calculated the risk for the first infection or reactivation of latent herpesviruses in patients treated with biologics compared to the control group. We found a twofold higher risk in patients treated with the monoclonal antibodies INF (HR: 2.1, p=0.01) or ADA (HR: 2.0, p=0.01). For patients who were treated with ETA the risk for reactivation of a herpes infection was only slightly higher than for patients in the control group (HR: 1.2, p=0.53).

Controlled for the disease activity (DAS28) at beginning of treatment (HR: 1.3, p<0.01) we found an increased risk for patients treated with INF or ADA (HR: 1.7, p=0.046) but no increase for patients treated with ETA (HR: 1.0, p=0.9).

Conclusion: Our data suggest a different mode of action of TNFα antibodies and the soluble TNF receptor fusion protein etanercept in respect to the reactivation of a latent herpes infection. In addition to an influence of the inflammatory activity of the disease TNFα inhibition by adalimumab or infliximab likely increases the hazard risk of (re-)occurrences of viral herpes infections.

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Strangfeld A, Listing J. Bacterial and opportunistic infections during anti-TNF therapy. *Best Pract Res Clin Rheumatol* 2006; 20(6):1181-1195