Leflunomide increases the risk for incident peripheral neuropathies in patients with RA

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Objectives: To estimate the hazard risk of incident peripheral neuropathy (PN) in patients with rheumatoid arthritis (RA) under various treatments.

Methods: Data of RA patients enrolled between May 2001 and December 2006 into the ongoing prospective cohort study RABBIT (German biologics register) were used for this analysis. In RABBIT, treatment, clinical status and adverse events are assessed at fixed time points of follow up. Patients with neurological symptoms at baseline were excluded. The risk of developing a PN (only confirmed diagnoses) was investigated using the Cox proportional hazard regression model. A patient was considered as being under risk of a specific treatment if she/he currently received this treatment or if it was terminated within the last month before the occurrence of neurological symptoms.

Results: Among the 5,022 patients included in the analysis, 1,243 received etanercept, 589 infliximab, and 1,417 adalimumab. In the control group 1,773 patients were enrolled with conventional DMARD treatment, 883 of them received leflunomide at baseline.

21 patients were newly diagnosed with PN. Patients who developed a PN were significantly older (60.0 versus 54.6 years) and more frequently men (38.1% vs. 21.7%). 12 of the 21 patients developed the neuropathy while they were treated with leflunomide corresponding to a rate of 4.4/1000 patient years (pyrs) (95% CI: 2.6 – 7.3). Corresponding rates for anti-TNF or methotrexate were 0.9 and 1.0/1000 pyrs respectively. Leflunomide treatment was discontinued in 8/12 patients. In two patients who continued treatment, PN was reported at subsequent follow-ups, in one patient PN reoccurred with the restart of leflunomide treatment after withdrawal.

Diabetes mellitus was found in 2 patients with PN (p=0.7). No patient had a concomitant renal or thyroid gland disorder.

Controlled for age, gender, disease activity, rheumatoid factor, and functional capacity a significantly increased risk for developing a PN was found for treatment with leflunomide (hazard ratio (HR): 3.1 (95%CI: 1.2 – 7.9), p=0.02) whereas treatment with MTX (HR: 0.38, p=0.05) or biologic agents (HR: 0.33, p=0.03) was associated with a significantly decreased risk.

Conclusion: The occurrence of peripheral neuropathies is increased in patients with higher age, male gender and high disease activity. The treatment with leflunomide is an independent risk factor. Therefore patients receiving leflunomide should be carefully monitored for the occurrence of this disabling adverse event.

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