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Rituximab and Leflunomide for Wegener's granulomatosis

A long term follow up

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Letter

Several case series und small uncontrolled studies on Rituximab (RTX) treatment for Wegener's granulomatosis (WG) refractory to standard treatment are available. However little is known about long time results for this treatment modality. This is an update of our patients (1) treated with RTX and concomitant leflunomide (LEF) after a follow up period of 48 (range 29-52) months.

Between June and December 2005 five consecutive patients with extensive WG resistant to cyclophosphamide were treated with RTX (375mg/m² weekly for 4 weeks) and a maintenance therapy with LEF (20mg/day). All patients were positive for c- and PR3-ANCAs. The Birmingham Vasculitis activity Score (BVAS) was used for clinical follow up and CRP, ESR and PR3-ANCAs (norm < 6 U/ml) for serological response assessment. Primary outcome measure in this retrospective analysis was the time to relapse (BVAS new > 1).

After 6 months 4/5 patients were in complete remission; 1 patient had a BVAS of 1 due to chronic sinusitis. Three patients experienced a total of 4 relapses and were re-treated with RTX (375mg/m² weekly for 4 weeks) after a median of 21 months (18-24). All three patients responded very well to the second and third course, respectively. Rituximab was well tolerated in all patients. One patient (no. 4) died at month 30 most probably due to a cardiac ischemia; autopsy was declined. In all relapsed patients PR3-ANCAs had increased prior to clinical relapse. 2 patients are still in remission after 38 and 48 months. In one patient still in remission LEF was switched to methotrexate due to diarrhoea (2-3 loose bowels/day) at month 18. Diarrhoea did not improve and was most probably due to a bowel resection years before. An infectious cause (including CMV) could be ruled out.

Smith et al (2) described 11 patients with systemic vasculitis (WG/microscopic polyangiitis/Churg Strauss vasculitis) in a cohort together with systemic lupus erythematosus patients with a median follow up of 23 months. 4/5 patients with WG achieved a remission and two relapses occurred after 17 and 20 months, respectively. Two patients were in ongoing remission after 18 and 21 months. ANCA titres tended to rise again in those who did have a relapse.

Stasi et al (3) reported on 10 RTX-treated patients with ANCA associated vasculitis and a follow up period of 33,5 months. No additional maintenance therapy was given and steroids were tapered. Only three patients experienced a relapse (after 12, 16 and 24 months), all responding well to re-treatment with RTX. Theese relapses were preceded by elevations in ANCA titres.

This is the first report on a long term observation over 4 years in patients with WG treated with RTX as induction treatment and LEF for maintenance. Stasi et al (3) had the lowest rate of relapses without using a maintenance treatment. However, data from cyclophosphamide studies suggest that a maintenance treatment after cyclophosphamide induction may reduce the rate of relapses (4,5). As the patient cohorts in the studies on Rituximab for ANCA associated vasculitis are very heterogeneous and small, a definite conclusion for the necessity of a maintenance treatment after induction with RTX is not possible yet. RTX appears to be a promising therapeutic option for cyclophosphamide resistant WG and is effective for re-treatment in case of relapse. A rise in ANCAs preceded most of the clinical relapses in the 3 studies with a longer follow up period, thus ANCA titres should be monitored.

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Figure 1a/b): Disease activity assessed by the Birmingham vasculitis activity score (BVAS) for new or worse manifestation showing 4 relapses in 3 patients (a) as well as the corresponding titres for PR3-ANCAs (b).