Low CD4/CD8 ratio is associated with lower immunoglobulin levels in granulomatosis with polyangiitis patients receiving Rituximab.

Background
Rituximab (RTX) is an effective B depleting agent for inducing and maintaining remission in patients with Granulomatosis with polyangiitis (GPA). RTX induced late onset neutropenia and hypogammaglobulinemia potentiates the risk of common infections, but infections mediated by T-cell dysfunction have also been described during RTX treatment.

Objective
To describe the course of CD4 cells and CD4/CD8 ratio in GPA patients during long term RTX treatment.

Methods
Analysis of prospectively collected data in 35 GPA patients treated with RTX between April 2004 and September 2011 at one centre. Total immunoglobulin (Ig) levels and immunophenotyping of lymphocytes were measured at RTX initiation and then after 3, 6, 12, 18 and 24 months. CD4 < 0.3 x 10^9/L and CD4/CD8 ratio < 1 were defined as low count and ratio. Patients (median age 50 (14-79), 46 % women) had received a cumulative dose cyclophosphamide of 14.8 g (0-250) were treated with a median RTX cumulative dose of 4 g (2-6). Results are expressed in means, unless mentioned otherwise. The student's t-test and the Mann-Whitney U test are used appropriately.

Results
The CD4 cell count decreased from 0.46 at baseline to respectively 0.38 (p=0.331), 0.41 (p=0.183) x 10^9/L at 3 and 6 months and afterwards increased to 0.57 (p=0.034) at 24 months. Ratio decreased from 1.31 to 0.99 (p=0.007) at 3 months and increased gradually to 1.62 (p=0.057) at 24 months. The proportion of patients with low CD4 decreased from 43 % at baseline to 18 % at 24 months while the proportion of patients with low ratio remained stable between 34 and 50 % (at 3 months) throughout the study period.
Patients with low CD4 at baseline had an increase in their CD4 cell count at 3 months (0.18 vs -0.28 x 10^9/L; p=0.003) while patients with normal CD4 cell count had a decrease. Consequently there were no statistical difference in CD4 cell count between the 2 groups at 3 months (0.36 vs 0.40 x 10^9/L; p=0.064).
Patients with low CD4 at baseline did not have lower level in total Ig throughout RTX maintenance, whereas patients with low ratio at baseline had (Table).
Two patients had severe infections in the first 24 months of RTX maintenance and 1 had an infection due to T-cell dysfunction (Pneumocystis jiroveci) 4 months after RTX initiation.

Conclusion
RTX treatment in GPA patients results in a temporary decrease in CD4 cell count and CD4/CD8 ratio for about six months. Patients with low baseline ratio remain low during RTX maintenance and are prone to lower Ig levels. The risk of infection due to T-cell dysfunction appears low in the first 2 years of RTX maintenance.

Table

Patients at baseline	Total immunoglobulin level g/L		
	Baseline	12 mo	24 mo
Low CD4	10.8	8.0	7.4
Normal CD4	11.8	9.2	8.3
p-value	0.283	0.158	0.179
Low ratio	11.8	7.6	7.1
Normal ratio	11.2	9.3	8.4
p-value	0.461	0.021	0.063