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VALIDATION OF B CELL DEPLETION AS A PREDICTOR OF CLINICAL RESPONSE AND EFFICACY OF RETREATMENT OF NON-RESPONSE IN RHEUMATOID ARTHRITIS

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Background: Rituximab has been licensed for the treatment of Rheumatoid Arthritis (RA) for over a decade. We previously showed that the initial depth of B cell depletion was associated with clinical response; 96% complete versus 74% incomplete depletion at 6 months (p=0.02)[1] and that retreatment of initial non-responders with incomplete depletion led to 72% response rate in cycle 2 (C2)[2].

Objectives: To validate B cell depletion after the first infusion as a predictor of response to rituximab (Project 1) and assess outcome of retreatment of first cycle non-responders (Project 2) as a basis for B cell monitoring during rituximab treatment.

Methods: The published discovery cohorts included 60 patients in Project 1 and 25 patients in Project 2. For this validation study, we analysed the subsequent consecutive 180 patients with RA treated with rituximab at a single centre. Each cycle of rituximab consisted of 2x1000mg infusions, repeated on clinical relapse. B cell subsets (naïve, memory and plasmablast) were measured at baseline, after first infusion of rituximab (2 weeks) and at early B cell repopulation (6 months) using a flow cytometry protocol optimized to detect low numbers of B cell subsets and plasmablasts. Complete depletion was defined as total B cell count $<0.0001 \times 10^9$/L. First cycle non-responders who had incomplete depletion at C1 were retreated at 6 months.

Results: 180 patients (Female=147(81%), median age at rituximab initiation 62(IQR 51-71) years and median disease duration 10(IQR 5-18) years were studied. 72(40%) patients were biologic-naïve. In C1, 126 (70%) achieved moderate-good EULAR response. The complete depletion rate for C1 was 54%. Complete depletion was associated with response; p=0.027 (Table 1).30 patients who were C1 non-responders and had incomplete depletion were retreated at 6 months. Of these, 20(67%) had complete depletion and 20(67%) responded in C2. Non-responders in C2 had trend to higher plasmablast numbers at retreatment than responders (p=0.14).

Table 1:B cell depletion and response in validation cohort

Project A				
Cohort	Depletion	Non Response	Response	p
Validation (n=180)	Incomplete	32/82 (39%)	50/82 (61%)	0.036
	Complete	23/98 (23%)	75/98 (77%)	
Combined Discovery + Validation (n=240)	Incomplete	46/117 (39%)	71/117 (61%)	0.003
	Complete	26/123(21%)	97/123 (79%)	

Conclusions: We have validated that the depth of B cell depletion after the first infusion is a predictor of response to rituximab in RA. A high degree of response in C2 was also confirmed when C1 non-responders who had incomplete depletion were retreated. B cell subsets therefore should be monitored in the routine care of RA patients receiving rituximab and repeat infusions considered if early depletion is incomplete and clinical response poor.

References: [1] Dass S et al. A&R 2008 [2] Vital EM et al. A&R 2010

Disclosure of Interest: None declared