Effectiveness of DMARD co-therapy in rituximab-treated rheumatoid athritis patients – Results of a one-year follow up study from the CERRERA collaboration

Cem Gabay[1] ,' Katerina Chatzidionysiou[2], E. Nasonov[3], Galina Lukina[3], Merete L. Hetland[4], Ulrik Tarp[4], Piet L.C.M. van Riel[5], Dan C. Nordström[6], J. Gomez-Reino[7], Karel Pavelka[8], Matija Tomsic[9], Elisabeth Lie[10], Tore K. Kvien[11], Ronald F. van Vollenhoven[2]

[1]Univ Hosp of Geneva, Switzerland, [2]Karolinska Univ Hosp, Stockholm, Sweden, [3]Institute of Rheumatology, Moscow, Russia, [3]DANBIO, University Hospital, Copenhagen, Denmark, [5]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [6]ROB-FIN Helsinki University Central Hospital, Helsinki, Finland, [7]Hospital Clinico Univ De Santiago, A Coruna, Spain, [8]Charles University, Prague, Czech Republic, [9]University Medical Center, Ljubljana, Ljubljana, Slovenia, [10]Diakonhjemmet Hospital, Oslo, Norway

Background: Clinical trials have shown that rituximab (RTX) is efficacious in rheumatoid arthritis patients when prescribed in combination with methotrexate (MTX). However, some patients do not tolerate MTX, and are treated either with other DMARDs such as leflunomide (LEF) or without co-therapy

Objective: To compare the effectiveness and safety of rituximab alone or in combination with either MTX or LEF.

Methods: Ten European registries submitted anonymized datasets with baseline, 3, 6, 9 and 12 month clinical data for patients who had started RTX. Baseline and follow-up data included disease duration, number of previous biologic agents, disease activity (DAS28), functional disability (HAQ), concomitant DMARDs, corticosteroid use, and RTX retreatment. Patients were separated into three groups: RTX+MTX, RTX+LEF, and RTX alone. Patients receiving other DMARDs or combinations of DMARDs were excluded. The frequency of EULAR good response was compared using ANOVA followed by Dunn/Bonferroni post-hoc testing, and by logistic regression.

Results: 1901 patients were analyzed: 1026 treated with RTX+MTX, 146 with RTX+LEF, and 429 with RTX alone. At baseline, RTX alone patients were older (55.4 ± 13.2 versus 52.6 ±12 and 52.4 ±13.3), had more previous biological agents (1.2±1.2 versus 0.8±1.1 and 1.1±1.1), and lower DAS28 values (5.9±1.2 versus 6.2±1.0 and 6.2±1.2) than LEF and MTX, respectively. Significantly more patients achieved a EULAR good response at 6 months when treated with RTX+LEF (33.3%) as compared to RTX+MTX (21.1%) and RTX alone (20.2%), *P*=0.01 and *P*=0.005, respectively. A similar trend was observed at 12 months. A shown in Table, LEF is significantly associated with a good EULAR response.

Univariate adjusted analysis	6 months		12 months	
	Lef vs Mtx	Lef vs None	Lef vs Mtx	Lef vs None
Coefficient	0.96	1.11	0.71	0.73
OR (95% CI)	2.61 (1.18-5.75)	3.05 (1.3-7.13)	2.03 (1.1-3.74)	2.08 (1.07-4.04)
p-value	0.017	0.010	0.02	0.03

Co-treatment with LEF was still predictive of a good EULAR response when taking into account the disease duration and number of previous biological agents in a multivariate analysis. Fewer patients with RTX + LEF were retreated during the first 12 months (10.9%) compared with RTX+MTX (20.2%) or RTX alone (18.9%). Adverse events occurred in 7.5%, 11.8%, and 12.4% of patients in RXT + LEF, RTX + MTX, and RTX alone, respectively.

Conclusion: The results of this large multinational cohort of patients show that LEF is an effective and safe alternative concomitant treatment with RTX in patients intolerant to MTX.