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Ther Adv Musculoskel Dis
2021, Vol. 13: 1–7
DOI: 10.1177/1759720X211009020

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Concomitant beta-blocker use is associated with a reduced rate of remission in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs: a *post hoc* multicohort analysis

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease associated with increased risk of cardiovascular disease (CVD). Treatment for CVD may involve pharmacological agents that antagonise beta adrenergic receptors. These receptors may play an important role in immunology, and the effects of beta-blockers (BB) in RA is unknown. The aim of this study was to investigate the association between BB use and remission in patients with RA initiating tocilizumab +/− conventional synthetic (cs-) DMARD therapy.

Methods: Data was pooled from five randomised trials investigating tocilizumab and/or csDMARD treatment in RA (primarily methotrexate). The association between BB use and remission according to the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) was assessed by Cox proportional hazard analysis. Sensitivity analysis in patients with pre-existing CVD and an exploratory analysis of the impact of other CVD drugs were conducted.

Results: Data were available from 5502 participants, 594 (10.8%) of whom were using systemic BB. BB use was associated with less frequent SDAI remission in the total [adjusted hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.57–0.87, $p = 0.001$] and CVD cohort [adjusted HR 0.72 (0.57–0.90, $p = 0.005$)]. The association was consistent between trials (interaction $p = 0.44$) and treatment arms (interaction $p = 0.06$). No significant association between remission and β1-receptor selectivity was identified ($p = 0.16$), and the association was independent from other cardiovascular drug use. Similar associations between BB use and CDAI remission were observed.

Conclusion: In a large, pooled cohort of RA patients initiating csDMARDs and/or tocilizumab, BB use was independently associated with less frequent remission.

Keywords: beta-blockers, DMARD, remission, rheumatoid arthritis, tocilizumab

Received: 12 March 2021; revised manuscript accepted: 18 March 2021.

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Introduction

Rheumatoid arthritis (RA) is the most prevalent autoimmune arthropathy and is associated with an increased risk of other systemic conditions, particularly cardiovascular disease (CVD), necessitating a variety of pharmacological and non-pharmacological therapies.[1] It is therefore unsurprising that patients with RA may be treated with beta-blockers (BB), yet the association between BB use and the efficacy of disease-modifying antirheumatic drugs (DMARDs) has been largely unexplored.

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Catecholamines can modulate the effects of immune effector cells *via* beta-adrenergic receptors (βAR). There are three types of βAR (β_1AR, β_2AR and β_3AR), and β_2AR are thought to play a key role in immunological balance and may influence the development of RA and/or disease activity in patients with established disease.[2–4] These effects appear to be dependent upon the cell type and stage of disease,[5] accelerating disease in the early stages, but leading to beneficial (immunosuppressive) effects in later stage RA.[2,4] It is not known if they modulate responses to DMARDs. In recent years, there has been a trend to use β_1-adrenergic receptor (β_1AR) selective BB for CVD as these receptors are concentrated in cardiac myocytes. These agents should therefore interact less with the immune system than non-selective BB. Given the potential interaction of BB with the immune system, the aim of this study was to use large, high-quality individual-participant data (IPD) collected in clinical trials to investigate the association between systemic use of concomitant BB and the likelihood of achieving remission in RA patients on conventional synthetic DMARDs (csDMARDs) or the biological DMARD tocilizumab.

Patients and methods

Patient population

IPD from the Hoffmann-La Roche sponsored phase III clinical trials LITHE [ClinicalTrials.gov identifier: NCT00106535] registered 28 March 2005, AMBITION [ClinicalTrials.gov identifier: NCT00109408] registered 28 April 2005), TOWARD [ClinicalTrials.gov identifier: NCT 00106574] registered 28 March 2005, FUN CTION [ClinicalTrials.gov identifier: NCT0 1007435] registered 20 August 2012, and SUMMACTA [ClinicalTrials.gov identifier: NC T01194414] registered 3 September 2010, were utilized in this pooled analysis. These studies were conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrolment. The secondary analysis of de-identified IPD, in the current study, was exempted from review by the Southern Adelaide Local Health Network, Office for Research and Ethics as it was classified as minimal risk research. Tocilizumab clinical trials were accessed according to Hoffmann-La Roche policy and have been made available through Vivli, Inc. (www.vivli.org).

LITHE included RA patients randomly assigned (1:1:1) to tocilizumab (4 or 8 mg/kg) plus MTX or MTX alone.[6] AMBITION included RA patients randomized 3:3:1 to tocilizumab (8 mg/kg), MTX (7.5 mg/week) or placebo for 8 weeks followed by tocilizumab (8 mg/kg).[7] TOWARD randomised patients 2:1 to either tocilizumab (8 mg/kg) or placebo, with both groups receiving concomitant csDMARD therapy.[8] FUNCTION included MTX-naïve patients with early progressive RA randomized 1:1:1:1 to tocilizumab (4 or 8 mg/kg) plus MTX, tocilizumab (8mg/kg) or MTX.[9] SUMMACTA included RA patients randomised 1:1 to tocilizumab-subcutaneous (tocilizumab-SC) 162 mg weekly or tocilizumab-intravenous (tocilizumab-IV) 8 mg/kg every 4 weeks for 24 weeks in combination with csDMARDs. To assess the long-term safety and efficacy of tocilizumab in an extension study of SUMMACTA, patients who received tocilizumab-SC in the first 24 weeks were randomised 11:1 to receive tocilizumab-SC or tocilizumab-IV and patients receiving tocilizumab-IV were randomized 2:1 to receive tocilizumab-IV or tocilizumab-SC.[10] Data were collected up to week 97 in the SUMMACTA extension study.[10]

All studies included adult patients (age $\geq$ 18 years) diagnosed with moderate-to-severe RA for $\geq$3 (AMBITION) or $\geq$6 months (all other studies) according to American College of Rheumatology (ACR) classification criteria. Active RA was defined by swollen joint count (SJC) $\geq$ 6 (66 joint count), tender joint count (TJC) $\geq$ 8 (68 joint count) and C-reactive protein (CRP) $\geq$ 1 mg/dl or erythrocyte sedimentation rate (ESR) $\geq$ 28 mm/h. FUNCTION included early progressive RA patients defined according to the 28-joint Disease Activity Score using the erythrocyte sedimentation rate (DAS28-ESR) over 3.2, with SJC $\geq$ 4, TJC $\geq$ 6, ESR $\geq$ 28 mm/h or CRP $\geq$ 1 mg/dl and positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies.

Predictors and outcomes

The primary outcome was time to first RA remission according to the Simplified Disease Activity Index (i.e. SDAI $\leq$ 3.3).[11] Time to first RA remission according to Clinical Disease Activity Index (i.e. CDAI $\leq$ 2.8) was the secondary outcome.[11] Patients were censored at the last known date of follow up or at the recorded date of death if they had not achieved remission. Systemic BB use at the time of initiating RA therapy (baseline) was

assessed as the primary predictor. The use of other cardiovascular medicines at baseline [i.e. calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), and thiazide diuretics] was assessed as secondary predictors.

Pre-treatment SDAI, CDAI, age, sex, race (white/Asian/black/other), RA disease duration, number of previous DMARDs, corticosteroid use, presence of hypertension, coronary artery disease and diabetes mellitus were available.

Individual components of the disease activity measures [28 tender (TJC) and swollen (SJC) joint counts, patient and physician assessment of disease activity and C-reactive protein (CRP)] were evaluated to identify the main factors driving altered rates of remission. Remission criteria for individual disease activity measures were based on the Boolean criteria proposed by Felson *et al.*,[11] whereby remission was defined for TJC as $\leqslant 1$, SJC $\leqslant 1$, and CRP $\leqslant 1$ mm/h. Although not included in Felson *et al.*,[11] physician assessment of disease activity $<10\%$ was classified as remission.

Statistical analysis

Cox proportional hazard analysis was used to assess the association between BB use and remission in the pooled cohort from five clinical trials. Results were reported as hazard ratios (HR) with 95% confidence intervals (95% CI). Statistical significance was set at $p < 0.05$ (likelihood ratio test). Univariable and adjusted analyses were conducted to assess the independence of associations from other prognostic factors. Complete case analysis was used. Analyses were stratified by study and treatment arms. Heterogeneity of the BB association according to treatment, study, or number of cardiovascular drugs (excluding BB) at baseline was assessed using a treatment-by-biomarker interaction term. Kaplan–Meier analysis was used for plotting and estimating remission probabilities.

A sensitivity analysis was conducted to determine the association of BB use with remission in patients with pre-existing CVD. Exploratory analysis of the likelihood of remission according to BB cardio-selectivity (β1AR-selective/non-selective) was performed. The association between remission and baseline use of CCB, ACEI/ARB, or thiazide diuretics was also explored. All analyses were conducted using R version 3.4.3.

Results

Patient population

Of the 5502 patients, 4126 (75%) were treated with tocilizumab ± csDMARDs and 1376 (25%) with csDMARDs alone, 594 (11%) of whom were using a BB, the majority of which (89%) were β_1AR-selective agents. A summary of patients' baseline characteristics stratified by study and BB use is provided in Supplemental Tables S1 and S2, respectively. A summary of BBs taken at baseline is presented in Supplemental Table S3. SDAI and CDAI were missing for 10 and 2 patients, respectively, and for SDAI and CDAI adjusted analysis, 143 (2.6%) and 100 (1.8%) patients, respectively, were excluded due to missing data.

Median follow up was 260 weeks in LITHE, 24 weeks in AMBITION, 24 weeks in TOWARD, 52 weeks in FUNCTION and 97 weeks in SUMMACTA.

Association between concomitant BB use and remission

BB use was associated with less SDAI-defined remission on univariable [(hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.52–0.76], $p < 0.001$, Supplemental Table S4] and adjusted analysis [HR 0.70 (0.57–0.87), $p = 0.001$, Table 1]. No significant heterogeneity in the identified association was observed between studies (SDAI-interaction $p = 0.44$), treatment arms (SDAI-interaction $p = 0.06$), or by the number of other cardiovascular drugs used (SDAI-interaction $p = 0.88$) (Supplemental Tables S5–S7). There was no significant difference in the rate of SDAI-remission between patients on β_1AR-selective and non-selective BB [adjusted HR 0.68 (0.40–1.16), $p = 0.16$, Table 2]. Similar associations between BB use and CDAI remission were observed (Tables 1 and 2, Supplemental Tables S4–S7). Kaplan-Meier estimates of remission likelihood according to BB use and BB selectivity are presented in Figure 1.

Although the use of CCB ($p = 0.006$) and ACEI/ARB ($p = 0.001$) were significantly associated with lower likelihood of achieving SDAI-remission on univariable analysis, no significant associations

Table 1. Adjusted pooled cohort analysis of the association between BB use and remission.

Pooled cohort	SDAI-remission			CDAI-remission		
	Events/patients	HR (95% CI)	*p*	Events/patients	HR (95% CI)	*p*
BB use						
No	1341/4769	1		1630/4815	1	
Yes	110/580	0.70 (0.57–0.87)	0.001	133/585	0.73 (0.60–0.88)	0.001

Adjustment variables: weight, age, race, sex, RA disease duration, presence of coronary artery diseases, hypertension, diabetes, corticosteroid use, baseline disease activity (SDAI, CDAI scores), and number of previous DMARDs.
BB, beta-blocker; CDAI, clinical disease activity index; CI, confidence interval; DMARDS, disease-modifying antirheumatic drugs; HR, hazard ratio; RA, rheumatoid arthritis; SDAI, simple disease activity index.

Table 2. Adjusted pooled cohort analysis of the association between BB selectivity and remission.

Pooled cohort	SDAI-remission			CDAI-remission		
	Events/patients	HR (95% CI)	*p*	Events/patients	HR (95% CI)	*p*
BB selectivity						
Non-selective	19/82	1		18/83	1	
β1-selective	91/498	0.68 (0.40–1.16)	0.157	115/502	1.04 (0.61–1.78)	0.871

Adjustment variables: weight, age, race, sex, RA disease duration, presence of coronary artery diseases, hypertension, diabetes, corticosteroid use, baseline disease activity (SDAI, CDAI scores), and number of previous DMARDs.
BB, beta-blocker; CDAI, clinical disease activity index; CI, confidence interval; DMARDS, disease-modifying antirheumatic drugs; HR, hazard ratio; RA, rheumatoid arthritis; SDAI, simple disease activity index.

between the use of CCB ($p=0.18$), ACEI/ARB ($p=0.22$), and thiazide diuretics ($p=0.83$) were identified on adjusted analysis. Similar associations were observed with CDAI-remission (Supplemental Tables S8 and S9).

The analysis of the individual components of the disease activity measures indicated tender joint count, and patient and physician assessments of disease activity were the primary drivers of reduced remission in patients on BB (Supplemental Table S10 and Supplemental Figure S1).

Sensitivity analysis

In the pooled cohort, 1949 (35%) had pre-existing CVD, 539 (28%) of whom were using a BB. In this subgroup, BB use was associated with lower remission on univariable (Supplemental Table S11) and adjusted analyses (Table 3). Kaplan–Meier estimates of remission likelihood according to BB selectivity are presented in Supplemental Figure S2.

Discussion

This study showed that BB use was associated with reduced likelihood of remission in five large independent cohorts of patients with RA who initiated tocilizumab and/or csDMARDs. No significant heterogeneity in the identified association was observed between studies, treatment arms, and the number of cardiovascular drugs used at baseline.

The role of βAR in autoimmune conditions has not been clearly established, although β_2AR appear to be most prominently involved. Further, Arthropathy associated with various BB has been reported in various case reports with metoprolol being the most frequently implicated.[12–14] In the present study, concurrent use of BB was associated with reduced likelihood of achieving remission but a difference in outcomes between those taking non-selective and β_1AR selective agents was not identified. Most patients in the analysis were taking β_1AR selective agents, suggesting that effects were mediated *via* interaction with β_1AR. β_1AR can inhibit the migration of innate immune cells

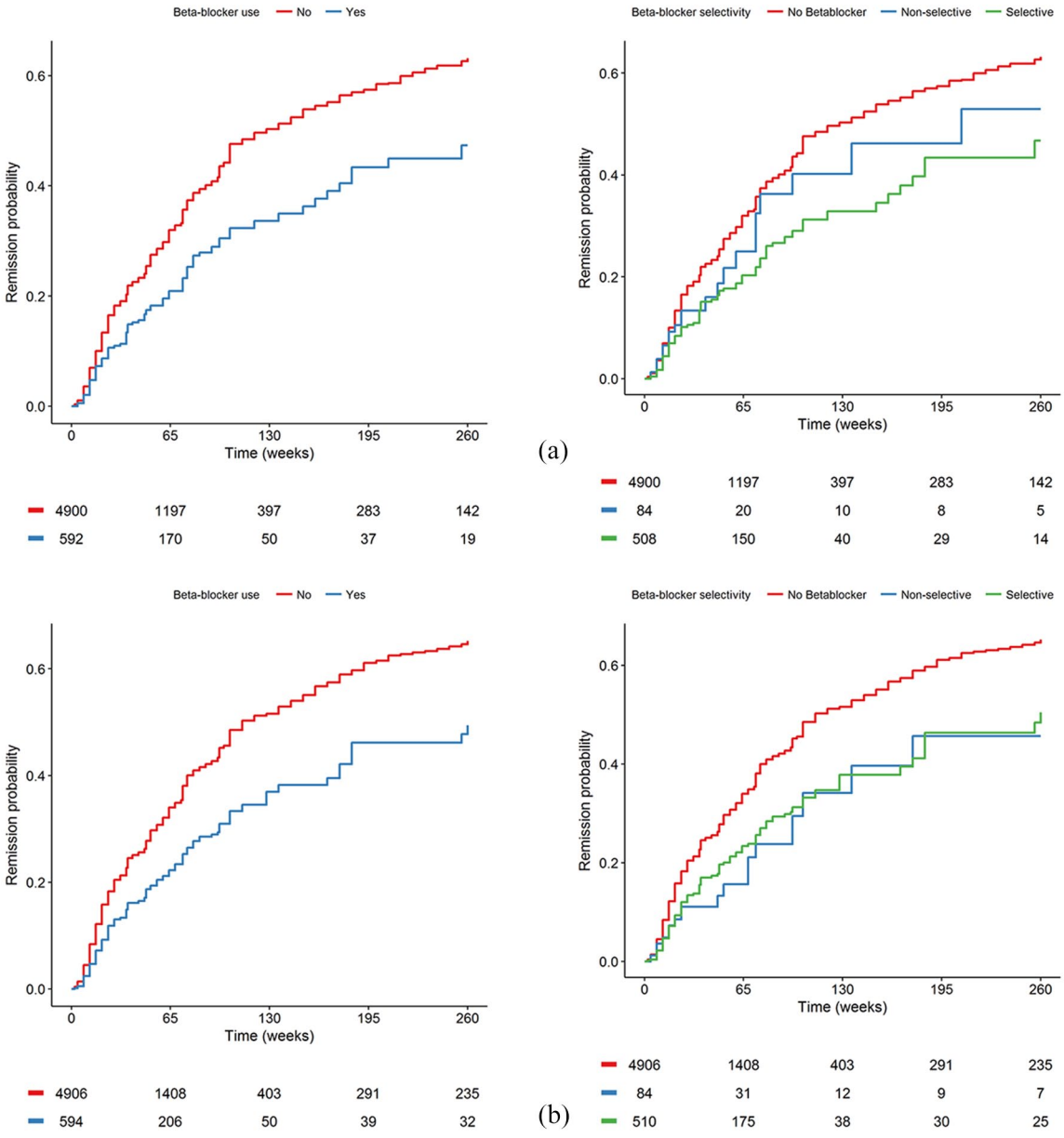

Figure 1. Kaplan–Meier estimates of the proportion of RA patients achieving remission at least once by BB use (top) and by BB selectivity (bottom) in the pooled cohort using (a) SDAI and (b) CDAI remission. The numbers underneath Kaplan–Meier plots indicate the absolute number of patients at risk by time.
BB, beta-blocker; CDAI, clinical disease activity index; RA, rheumatoid arthritis; SDAI, simplified disease activity index.

and, in murine models, mice deficient in β_1AR have improved bacterial defences – both of which are suggestive of catecholamines having an immunosuppressive role,[15] although β_1AR stimulation has also been shown to induce the production of proinflammatory IL-1β in monocytes.[16] However, the results of this analysis are inconsistent with a small study in patients with severe RA where the non-selective BB propranolol was associated with an improvement in some manifestations of disease in 10 of 11 patients, although this study was not controlled, patients had very advanced disease, the markers used to measure disease activity were not contemporary and other therapy was not reported.[17] The results presented herein may indicate a role for β_1AR pathways in RA pathophysiology, but this mechanism is yet to be confirmed and is uncertain given that β_1AR are located primarily

Table 3. Adjusted analysis of the association between BB use and remission in patients with pre-existing CVD (sensitivity cohort).

Sensitivity cohort	SDAI-remission			CDAI-remission		
	Events/patients	HR (95% CI)	*p*	Events/patients	HR (95% CI)	*p*
BB use			0.005			0.004
No	377/1372	1		424/1384	1	
Yes	99/527	0.72 (0.57–0.90)		118/532	0.73 (0.59–0.91)	

Adjustment variables: weight, age, race, sex, RA disease duration, presence of coronary artery diseases, hypertension, diabetes, corticosteroid use, baseline disease activity (SDAI, CDAI scores), and number of previous DMARDs.
BB, beta-blocker; CDAI, clinical disease activity index; CI, confidence interval; CVD, cardiovascular disease; DMARDS, disease-modifying antirheumatic drugs; HR, hazard ratio; RA, rheumatoid arthritis; SDAI, simple disease activity index.

on cardiac myocytes and may be downregulated in chronic inflammation.[18]

The large number of patients included in this analysis and the completeness of data collected are strengths of this study as they allowed for a relatively high-powered analysis. However, despite the large number of patients, there were comparatively few who took non-selective compared with β_1AR selective BB. The lack of difference in effect between β_1AR selective and non-selective BB may be due to low power in the subgroup analysis.

The limitations of this study include the lack of information regarding the dosage or duration of BB use, and subsequent inability to determine if these variables conferred a different response. This may be pertinent given that BB may be less effective in patients with RA and other autoimmune conditions due to the down-regulation of βAR, which may necessitate a higher dose.[18] Another potential limitation is that the study included data for tocilizumab as a bDMARD. Confirming the association for other bDMARDs is a future direction of the research. In all included studies, tocilizumab was administered intravenously except for the SUMMACTA study where TCZ was administered *via* subcutaneous injection. However, intravenous and subcutaneous tocilizumab have similar retention and effectiveness in patients with rheumatoid arthritis.[19]

The key implication of our findings is that the association between BB use and remission should be explored further to both confirm our findings and determine the pharmacological basis for the class effect, with future research focussing on determining differences between β_1AR selective and non-selective BB.

Authors contributions

A.Y.A, AMB, M.J.S, S.P, D.J.R.F, M.D.W. and A.M.H and were involved in the data analyses, interpretation of results, and writing the manuscript. A.Y.A, A.M.H. and M.D.W were involved in the concept and acquisition of the data. All authors read and approved the final manuscript

Conflict of interest statement

M.J.S is supported by Beat Cancer Research Fellowships from Cancer Council South Australia. A.M.H is supported by a Postdoctoral Fellowship from the National Breast Cancer Foundation, Australia (PF-17-007). All other authors declare no conflict of interest with the scientific content of the manuscript.

Ethical statement

This publication is based on research using de-identified individual participant data from data contributor Hoffmann-La Roche that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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