PREDICTORS OF CLINICAL RESPONSE TO BIOLOGICS IN RHEUMATOID ARTHRITIS: EXPERIENCE FROM CANADIAN CLINICS

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INTRODUCTION: Rheumatoid arthritis (RA) is an autoimmune disease affecting more than 300,000 Canadians. Untreated, the disease leads to irreversible joint damage and permanent loss of function. Multiple treatment options exists and response to those is inconsistent amongst patients. No uniform predictors of response have been established.

OBJECTIVES: The purpose of this study was to explore the predictors of clinical response in RA patients followed at Canadian clinics.

METHODS: We performed a 3-year prospective cohort study using RHUMADATA® registered RA patients followed at the IRM (Montreal), the *Centre d'ostéoporose et de rhumatologie de Québec* (Quebec City), and the *Centre de rhumatologie de l'est du Québec* (Rimouski). Selected subjects were 18 years of age or older consenting to the study and had been treated with at least one biologic agent (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab or anakinra) since 2003, had been followed for a minimum of one year before biologic therapy initiation and had a minimal follow-up of six months after biologic therapy. Socio-demographic (age, sex, type of drug coverage, education, type of work, and family income), clinical (comorbidities, co-therapy, physical function), disease characteristics (duration, rheumatoid factor, anti-CCP) and activity (DAS, CDAI and SDAI scores, SJC, TJC, ESR, CRP, morning stiffness duration, global patient and physician assessments) were measured at baseline. Patients reaching remission or low disease activity (LDA) according to the Disease Activity Score (DAS)-28 or the Clinical Disease Activity Index (CDAI) score were considered to have demonstrated a clinical response. More specifically, a DAS-28 score of ≤2.6 or a CDAI score of ≤2.8 were considered as remission, while a DAS-28 score of ≤3.2 or a CDAI score of ≤10 were considered as LDA. The association between baseline variables and clinical response to the first biologic at 6, 12, 24 and 36 months was assessed separately using univariate logistic regression models.

RESULTS: In all, 623 eligible patients were treated with at least one biologic (mean age 53.2 years, 77% women, mean disease duration 7.7 years). Because of missing DAS-28 and CDAI values, clinical response to biologic therapy after 6, 12, 24, and 36 months could be determined for 108 (17%), 100 (16%), 59 (9%), and 29 (5%) patients, respectively. In univariate analyses, baseline HAQ score [odds ratio (OR): 0.31; 95% confidence interval (CI): 0.13-0.72] was associated with remission at 6 months, while gender (women vs men; OR: 0.25; 0.07-0.90), employment status [unemployed vs full time (OR: 0.21; 0.05-0.86) and on sick leave vs full time (OR: 0.08; 0.01-0.91)], patient assessment of fatigue (OR: 0.83; 0.71-0.98), and patient global assessment (OR: 0.78; 0.63-0.97) were associated with LDA. ESR values were associated with remission at 12 months (OR: 0.96; 0.94-0.99). Variables associated with LDA at 12 months were physician global assessment of disease (OR: 1.28; 1.06-1.57) and use of methotrexate (OR: 0.28; 0.09-0.88). At 24 months, the number of DMARDs used (OR: 0.28; 0.09-0.84) and concurrent use of methotrexate and hydroxychloroquine (0.12; 0.03-0.56) were associated with LDA while only concurrent use of methotrexate and hydroxychloroquine (OR: 0.25; 0.07-0.82) was associated with remission. At 36 months, CRP (OR: 0.08; 0.01-0.83) and positive rheumatoid factor (OR: 0.02; 0.002-0.30) were associated with remission while no variables were found to be associated with LDA.

Baseline characteristics*

N	623
Age (years)	53.2 (12.4)
Women (%)	77.1%
Disease duration (years)	7.7 (8.3)
HAQ score	1.3 (0.6)
Fatigue (VAS)	4.5 (3.5)
Pain (VAS)	5.0 (3.3)
Morning stiffness (minutes)	92.8 (234.5)
Patient global assessment (VAS)	4.6 (2.9)
Physician global assessment (VAS)	2.0 (2.8)
CRP (mg/L)	13.0 (20.2)
ESR (mm/hr)	23.5 (20.9)
RF+ (%)	63.4%
Anti-CCP+ (%)	58.7%
DAS28-4(ESR)	4.1 (1.3)
CDAI	24.3 (13.2)

* Data are presented as means (SD), unless stated otherwise.

Selected predictors of clinical response to biologics

	Remission				Low disease activity			
	6 month	12 month	24 month	36 month	6 month	12 month	24 month	36 month
Age	0.99 (0.96-1.02)	1.00 (0.97-1.04)	1.00 (0.96-1.05)	0.95 (0.87-1.03)	1.00 (0.97-1.03)	1.01 (0.98-1.05)	0.98 (0.92-1.04)	1.00 (0.92-1.08)
Sex (women vs men)	0.44 (0.17-1.13)	0.52 (0.19-1.38)	0.69 (0.19-2.47)	0.50 (0.07-3.74)	0.25 (0.07-0.90)	0.46 (0.12-1.72)	1.91 (0.41-8.83)	ne
Disease duration (years)	0.98 (0.94-1.03)	1.00 (0.96-1.05)	0.99 (0.93-1.05)	0.97 (0.88-1.07)	0.98 (0.94-1.02)	1.03 (0.97-1.09)	0.97 (0.89-1.04)	0.97 (0.88-1.08)
HAQ score	0.31 (0.13-0.72)	1.39 (0.67-2.88)	0.98 (0.36-2.64)	0.11 (0.01-1.19)	0.46 (0.19-1.08)	1.30 (0.53-3.19)	0.59 (0.16-2.16)	0.46 (0.07-3.18)
Employment								
At home vs full time work	0.32 (0.10-1.07)	0.83 (0.28-2.47)	0.76 (0.18-3.17)	0.48 (0.06-3.99)	0.34 (0.10-1.14)	1.33 (0.38-4.69)	3.46 (0.28-42.62)	1.14 (0.06-21.87)
On sick leave vs full time work	ne	ne	0.63 (0.03-12.41)	ne	0.08 (0.01-0.91)	ne	ne	ne
Unable to work vs full time work	ne	ne	0.31 (0.02-4.41)	1.67 (0.07-37.73)	ne	0.59 (0.08-4.12)	0.09 (0.01-1.55)	0.14 (0.00-4.61)
Retired vs full time work	0.66 (0.22-1.98)	1.40 (0.48-4.07)	0.94 (0.17-5.07)	0.56 (0.04-8.09)	0.70 (0.19-2.52)	2.74 (0.65-11.50)	0.73 (0.08-6.31)	0.43 (0.02-9.36)
Unemployed vs full time work	0.20 (0.04-1.05)	2.00 (0.32-12.51)	0.21 (0.02-2.60)	ne	0.21 (0.05-0.86)	1.96 (0.20-19.15)	0.55 (0.04-8.27)	ne
Part time work vs full time work	1.21 (0.24-6.10)	ne	ne	ne	0.63 (0.10-3.83)	0.78 (0.06-9.74)	0.36 (0.02-6.19)	0.29 (0.01-6.91)
Student vs full time work	0.91 (0.05-15.49)	ne	ne	ne	ne	ne	ne	ne
Fatigue score (VAS 1-10)	0.93 (0.81-1.06)	0.94 (0.81-1.08)	0.98 (0.80-1.21)	0.64 (0.39-1.05)	0.83 (0.71-0.98)	0.91 (0.76-1.09)	0.87 (0.65-1.15)	0.66 (0.41-1.04)
Pain score (VAS 1-10)	0.88 (0.75-1.02)	0.97 (0.83-1.13)	0.97 (0.79-1.19)	0.82 (0.55-1.22)	0.96 (0.82-1.13)	0.96 (0.79-1.17)	0.75 (0.54-1.05)	0.76 (0.48-1.22)
Patient global assessment (VAS 1-10)	0.86 (0.72-1.03)	0.95 (0.79-1.14)	0.97 (0.74-1.27)	0.56 (0.30-1.03)	0.78 (0.63-0.97)	0.97 (0.76-1.22)	0.85 (0.59-1.23)	0.67 (0.37-1.21)
Physician global assessment (VAS 1-10)	1.05 (0.92-1.21)	1.15 (0.99-1.33)	1.09 (0.89-1.32)	1.10 (0.81-1.49)	1.02 (0.88-1.17)	1.29 (1.06-1.57)	1.01 (0.77-1.32)	1.28 (0.86-1.90)
Morning stiffness (min)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	0.96 (0.91-1.02)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Number of current DMARDs	1.06 (0.65-1.72)	0.88 (0.52-1.49)	0.58 (0.29-1.16)	0.82 (0.25-2.67)	0.67 (0.40-1.13)	0.55 (0.28-1.07)	0.28 (0.09-0.84)	0.48 (0.12-1.94)
Current use of methotrexate (yes vs no)	1.02 (0.46-2.24)	0.66 (0.29-1.51)	0.36 (0.12-1.11)	0.19 (0.03-1.08)	0.75 (0.32-1.73)	0.28 (0.09-0.88)	0.16 (0.02-1.37)	ne
Current use of hydroxychloroquine (yes vs no)	1.39 (0.62-3.10)	1.50 (0.67-3.38)	0.47 (0.16-1.34)	1.50 (0.27-8.35)	0.69 (0.30-1.60)	1.03 (0.40-2.65)	0.25 (0.06-1.08)	0.88 (0.13-5.94)
Current use of methotrexate and hydroxychloroquine (yes vs no)	1.37 (0.58-3.26)	1.43 (0.59-3.48)	0.25 (0.07-0.83)	1.07 (0.16-7.06)	0.54 (0.22-1.31)	0.67 (0.25-1.80)	0.12 (0.03-0.56)	0.56 (0.08-3.97)
Current use of corticosteroids (yes vs no)	ne	8.33 (0.99-70.48)	1.73 (0.37-8.03)	2.00 (0.27-14.99)	ne	ne	0.56 (0.10-3.28)	1.05 (0.10-11.63)
Anti-CCP (negative vs positive)	1.26 (0.47-3.39)	0.57 (0.20-1.63)	0.53 (0.13-2.10)	8.00 (0.66-97.31)	1.03 (0.38-2.81)	0.47 (0.14-1.64)	0.30 (0.04-2.11)	0.88 (0.05-16.74)
Rheumatoid factor (negative vs positive)	0.57 (0.25-1.30)	0.47 (0.19-1.20)	0.48 (0.14-1.68)	0.02 (0.00-0.30)	0.80 (0.33-1.96)	0.32 (0.09-1.18)	0.27 (0.03-2.38)	ne
CRP (< 10 mg/L vs >= 10 mg/L)	0.65 (0.29-1.47)	0.93 (0.42-2.05)	1.24 (0.43-3.58)	0.08 (0.01-0.83)	0.80 (0.33-1.90)	0.66 (0.26-1.71)	1.57 (0.39-6.32)	0.50 (0.08-3.32)
ESR (mm per hr)	1.00 (0.98-1.02)	0.96 (0.94-0.99)	0.99 (0.96-1.01)	1.01 (0.95-1.07)	1.01 (0.99-1.04)	0.99 (0.96-1.02)	0.99 (0.95-1.03)	0.97 (0.92-1.03)
Tender joint count (1-28)	0.94 (0.87-1.01)	0.99 (0.93-1.05)	0.96 (0.89-1.05)	0.83 (0.65-1.05)	0.95 (0.89-1.01)	0.97 (0.91-1.04)	1.01 (0.90-1.13)	0.98 (0.87-1.11)
Swollen joint count (1-28)	0.98 (0.90-1.06)	0.95 (0.88-1.01)	0.98 (0.89-1.08)	0.92 (0.76-1.12)	1.02 (0.94-1.10)	0.92 (0.86-1.00)	0.97 (0.85-1.10)	1.00 (0.85-1.18)
Hypertension (yes vs no)	0.75 (0.31-1.83)	1.16 (0.51-2.68)	1.64 (0.50-5.40)	ne	1.27 (0.50-3.27)	1.26 (0.47-3.43)	3.60 (0.42-31.12)	0.88 (0.13-5.94)
Hyperlipidemia (yes vs no)	0.39 (0.12-1.30)	0.52 (0.19-1.37)	1.39 (0.42-4.67)	ne	0.48 (0.17-1.36)	0.80 (0.27-2.35)	1.30 (0.24-6.97)	ne
Arthrosis (yes vs no)	0.74 (0.33-1.62)	1.26 (0.57-2.82)	0.60 (0.20-1.79)	3.20 (0.58-17.72)	0.74 (0.33-1.67)	1.86 (0.69-5.02)	0.66 (0.16-2.69)	0.88 (0.13-5.95)
Endocrinopathy (yes vs no)	0.78 (0.24-2.52)	0.68 (0.24-1.97)	1.20 (0.32-4.47)	ne	0.60 (0.19-1.87)	1.58 (0.41-6.05)	ne	ne
Diabetes (yes vs no)	0.19 (0.02-1.60)	0.67 (0.18-2.52)	1.73 (0.37-8.03)	ne	0.45 (0.11-1.91)	3.09 (0.37-25.72)	ne	ne
Cardiovascular disease (yes vs no)	0.39 (0.12-1.30)	0.52 (0.19-1.37)	1.39 (0.42-4.67)	ne	0.48 (0.17-1.36)	0.80 (0.27-2.35)	1.30 (0.24-6.97)	ne
Depression (yes vs no)	0.56 (0.10-3.04)	0.77 (0.16-3.62)	ne	ne	0.33 (0.07-1.57)	0.39 (0.08-1.88)	0.19 (0.01-3.28)	ne
COPD (yes vs no)	ne	1.04 (0.06-17.13)	ne	ne	ne	ne	ne	ne
Extra-articular manifestation (yes vs no)	0.72 (0.06-8.20)	0.33 (0.03-3.32)	ne	ne	0.96 (0.08-10.93)	0.30 (0.04-2.23)	0.19 (0.01-3.28)	ne

* ne = cannot be estimated

CONCLUSIONS: The results of this real-world study suggest that many clinical (HAQ score, DMARD use, fatigue, and patient and physician global assessments), laboratory (ESR, CRP and rheumatoid factor positivity) and socioeconomic characteristics (gender and employment status) may predict the response to biologics in RA patients. However, these variables were inconsistent between the different time points assessed. Future multivariate analyses will enable to confirm the predictors of clinical response to biologics in this population. Ultimately, better understanding of those predictors could help optimize the treatment of RA patients.

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