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Original article

Effect of disease duration and other characteristics on efficacy outcomes in clinical trials of tocilizumab for rheumatoid arthritis

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Abstract

Objective. To determine the extent to which disease duration, alone or in combination with other baseline clinical and non-clinical factors, explains variations in outcome of tocilizumab initiated in biologic-naïve patients with established RA.

Methods. In this pooled analysis of phase 3 and 4 clinical trials conducted by the sponsor, predictors of response, including demographics, disease characteristics at baseline (start of tocilizumab dosing) and study characteristics (e.g. patient inclusion criteria, tocilizumab dosing regimen) were evaluated. Response was measured as change from baseline to week 24 in Clinical Disease Activity Index (CDAI) and HAQ–Disability Index (HAQ-DI) scores and as the proportions of patients who experienced ≥50% improvement based on ACR criteria (ACR50) and CDAI remission (≤2.8) rates at week 24.

Results. Improvements in all outcomes investigated were observed in patients receiving tocilizumab. Although disease duration was statistically significant in the models, it accounted for <2% of variation in CDAI and HAQ-DI score changes from baseline to week 24; baseline CDAI and HAQ-DI values accounted for 32% and 15% of variations, respectively. Doubling of disease duration reduced the odds of achieving an ACR50 response by only 9%, and each additional 5-year period of disease duration decreased the odds of achieving CDAI remission by only 15%.

Conclusion. RA duration, alone or in combination with other baseline characteristics, had a statistically significant but clinically small effect on the outcomes of tocilizumab initiated in biologic-naïve patients with established RA.

Key words: biological therapies, clinical trials and methods, cytokines and inflammatory mediators, DMARDs, rheumatoid arthritis

CLINICAL SCIENCE

Introduction

The addition of a biologic to conventional synthetic DMARD (csDMARD) treatment regimens of patients with RA allows those who have inadequate responses the potential to achieve low disease activity and remission. Although the efficacy and safety of biologics are well established in csDMARD-inadequate responder (IR) patients with RA, predictors of response are less well recognized.

Results from observational studies, registry data and retrospective analyses indicate that duration of RA is a predictor of response to treatment; patients are more likely to achieve remission or sustained remission if csDMARD and/or biologic treatment is initiated earlier in their disease course [1–12]. In real-world clinical practice, patients whose disease duration is <5 years and who are receiving csDMARDs, alone or in combination with biologics, have the greatest likelihood of achieving remission according to DAS assessing 28 joints (DAS28) and Clinical Disease Activity Index (CDAI), although the odds of achieving remission decrease with longer duration of disease [1]. Other characteristics reportedly associated with achievement of remission include baseline levels of physical function and quality-of-life outcomes [HAQ–Disability Index (HAQ-DI) and the 36-Item

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Rheumatology key messages

- Disease duration had statistically significant but clinically small effects on efficacy outcomes with tocilizumab treatment.
- Quantified effects and *P*-values are important to evaluate practical implications of predictors of response.

Short Form Health Survey, respectively] and of disease activity measures [2, 4, 6, 8, 11, 13].

Tocilizumab, a humanized anti-IL-6 receptor-α mAb, has been approved for the treatment of patients with RA, GCA, polyarticular and systemic JIA and cytokine release syndrome; its long-term efficacy, safety and tolerability are well established in RA [14–16].

The aim of this study was to investigate the extent to which disease duration alone and in combination with other variables, such as inflammation, disease burden and other baseline factors, might explain variations in clinical outcomes in biologic-naïve patients with RA who are treated with tocilizumab.

Methods

Patients

Data were pooled from all phase 3 and 4 clinical studies conducted by the sponsor that met the selection criteria; in all there were 12 studies. Patients with established RA were included who initiated i.v. or s.c. tocilizumab treatment either as monotherapy or in combination with MTX/csDMARDs (Table 1) [17–28]. To ensure that pooled patients were all at a similar stage of therapy (i.e. that tocilizumab was their first biologic) and because the intention was to look into the effect of disease duration within a specific treatment line, patients with previous exposure to biologics were excluded from this analysis. All patient data from the trials were imported into one data set, as similarity of study protocols, schedules of treatment and assessment and patient selection criteria allowed for pooling on the patient level. All included studies had been conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, or both, and had been approved by the ethics committees/institutional review boards of the investigational centres as published. All patients provided written informed consent to participate in the individual studies.

Assessments

Characteristics considered potential predictors of response are shown in supplementary Table S1, available at *Rheumatology* online, and include demographic and patient characteristics (age, sex, region, race, weight, height, BMI and tobacco use), baseline disease and therapy characteristics [disease duration, number of previous csDMARDs (confounded with study), previous MTX use (confounded with study), glucocorticoid use and dose, DAS28 joint count, HAQ-DI, Routine Assessment of Patient Index Data 3 (RAPID3), CDAI, CRP, RF status, patient pain visual analogue scale, patient global health visual analogue scale, physician global health visual analogue scale, tender joint count, swollen joint count and ESR] and study medication characteristics [tocilizumab administered i.v. every

Table 1 Studies included in the analysis

Study	Patient population	Patients who received tocilizumab, *n*
ACT-RAY [17]	MTX-IR	552
ACT-STAR [18]	csDMARD-IR	145
ACT-SURE [19]	csDMARD-IR	949
ADACTA [20]	MTX-IR or MTX-intolerant	161
AMBITION [21]	MTX-naïve or MTX-free for ≥6 months[a]	143
BREVACTA [22]	csDMARD-IR	358
COMP-ACT [23]	csDMARD-IR	624
LITHE [24]	MTX-IR	353
OPTION [25]	MTX-IR	194
ROSE [26]	csDMARD-IR	253
SUMMACTA [27]	csDMARD-IR	1070
TOWARD [28]	csDMARD-IR	660
Total	–	5462

[a]Included patients with previous exposure to MTX who had discontinued MTX for reasons other than toxicity or lack of efficacy. csDMARD-IR: conventional synthetic DMARD inadequate responders; MTX-IR: MTX inadequate responders.

4 weeks or s.c. weekly or every 2 weeks (per study) and tocilizumab monotherapy or combination therapy with MTX or other csDMARDs]. RF status was not assessed in three studies (ROSE, ACT-STAR and ACT-SURE) and was available only in a minority of patients in ACT-RAY, HAQ-DI data were not assessed in two studies (ROSE and ACT-STAR) and BMI was not assessed in one study (ACT-SURE).

Outcomes of these pooled analyses were change from baseline to week 24 in CDAI and HAQ-DI and proportion of patients with ≥50% improvement in ACR criteria (ACR50 response) and CDAI remission (CDAI ≤2.8) rates at week 24.

Statistical analysis

Using a combination of clinically informed and mathematically driven variable-selection techniques, models were built to optimally fit and explain outcome variance. Mixed-model analysis of covariance (ANCOVA) with predictors as fixed effects and 'study' as a random effect to account for intracorrelation of observations within each study was used to model continuously distributed outcomes (week 24 score or change from baseline in CDAI and HAQ-DI) and estimate the least squares mean at week 24. A logistic regression approach was used to model binary outcomes (achievement or not of ACR50 and of CDAI remission at week 24), also using 'study' as a random effect in addition to the predictors. The effect of disease duration on outcomes was examined by estimating outcomes without any predictor, with RA duration at baseline as the only predictor and with RA duration plus additional baseline predictors. The effect of the baseline values of each continuously distributed outcome (i.e. HAQ-DI, CDAI) on the week 24 outcomes was explored by comparing the fit of models with only the baseline value of the outcome (i.e. unadjusted models) with those of models that also included other covariates (i.e. adjusted models).

Model fit was optimized by applying Bayes information criterion for ANCOVA and quasi-Akaike information criterion for logistic regression; models with the lowest Bayes information criterion and quasi-Akaike information criterion values were preferred. Explained outcome variance was operationalized by the residual variance method (ANCOVA) and Harrell's C (logistic regression), respectively. To further determine the unique contribution of RA duration, models including only the baseline value of the outcome (if statistically significant; $P < 0.05$) were compared with those including only RA duration and those excluding all RA duration parameters. SAS version 9.2 (SAS Institute Inc, Cary, NC, USA) was used to perform all analyses.

Results

Baseline demographics and disease characteristics

In total, 5462 tocilizumab-treated patients from 12 studies (Table 1) were included in the statistical analyses: MTX-IR ($n = 1099$), csDMARD-IR ($n = 4059$), MTX-naïve or MTX-free for ≥6 months ($n = 143$), and MTX-intolerant ($n = 161$).

Baseline (i.e. before initiation of tocilizumab) demographics and patient and disease characteristics are presented according to RA duration categories in Table 2. Patients with longer disease duration were older and had been exposed to more csDMARDs than patients with shorter disease duration. Use of glucocorticoids was similar across the disease duration categories, with approximately half the patients using glucocorticoids at baseline. Patients with disease duration >5 years had a higher prevalence of RF positivity and slightly higher mean HAQ-DI scores than those with shorter disease duration. Three-quarters of the patients were from Europe and North America.

Effect of baseline characteristics on outcomes after tocilizumab treatment

In all outcomes investigated, improvements were observed in patients receiving tocilizumab treatment (Figs. 1 and 2). Statistical modeling showed that from baseline to week 24, disease duration accounted for <2% of the variation in changes of HAQ-DI (Table 3, Fig. 1) and CDAI (Table 3, Fig. 2). The overall mean (S.D.) change from baseline to week 24 in HAQ-DI was –0.54 (2.07). The mean change decreased with increasing disease duration, indicating that patients with RA of longer duration experienced smaller improvements (Fig. 1). In the unadjusted model that only included baseline HAQ-DI as predictor, 15% of the variation in HAQ-DI change from baseline was explained. When comparing the adjusted models with and without RA duration, RA duration explained an estimated 1.7% of the variation in HAQ-DI change from baseline to week 24. Among the variables tested, variation in change from baseline to week 24 in HAQ-DI in the adjusted model was influenced, alone or in interaction terms, by baseline HAQ-DI, RA duration, CRP level, body weight, region, age and sex (Table 3).

The overall mean (S.D.) change from baseline to week 24 in CDAI was –23.5 (33.3). The unadjusted model that included only baseline CDAI explained 32% of this change. In the adjusted model that included RA duration plus additional baseline predictors, the explained variance was 35.4%. In the model with RA duration and interactions involving RA duration removed, the explained variance was 35.2%, which means that disease duration accounted for only 0.2% additional variation in CDAI change from baseline to week 24. Among the variables tested, variation in change from baseline to week 24 in CDAI in the adjusted model was influenced significantly, alone or in interaction terms, by baseline CDAI, CRP level, RAPID3, RA duration, glucocorticoid use, number of previous csDMARDs, region, age, sex and body weight (Table 3, Fig. 2). This more comprehensive model explained only an additional 3.7% of variance in change of CDAI, compared with the model with only baseline CDAI.

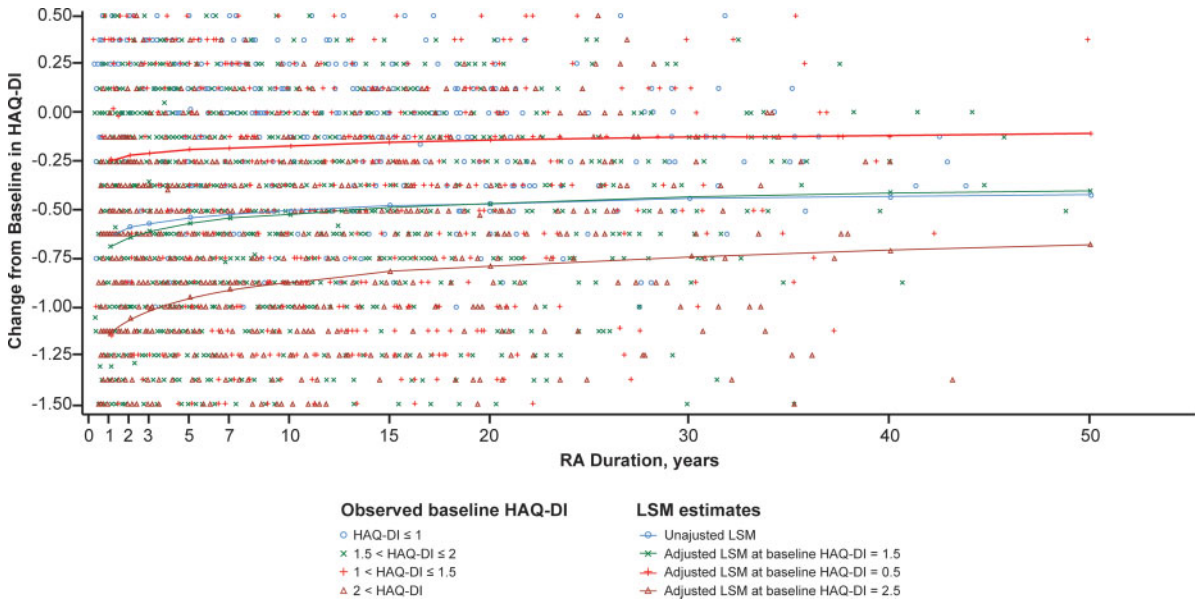
In total, 11.5% (629/5462) of patients achieved CDAI remission by week 24. The odds of achieving CDAI

Table 2 Baseline characteristics of tocilizumab-treated patients ($N = 5462$)[a], classified according to RA duration

Baseline characteristics	RA duration					
	<6 months, $n = 44$	6 months–2 years, $n = 1279$	>2–5 years, $n = 1274$	>5–10 years, $n = 1173$	>10 years, $n = 1692$	All patients, $n = 5462$
Female, *n* (%)	35 (79.5)	982 (76.8)	1027 (80.6)	962 (82.0)	1414 (83.6)	4420 (80.9)
White, *n* (%)	36 (81.8)	1037 (81.1)	1012 (79.4)	901 (76.8)	1381 (81.6)	4367 (80.0)
Age, mean (S.D.), years	51.1 (15.1)	51.7 (13.2)	51.5 (12.9)	52.3 (12.4)	56.7 (10.3)	53.3 (12.3)
Region, *n* (%)						
Europe	21 (47.7)	450 (35.2)	508 (39.9)	507 (43.2)	670 (39.6)	2156 (39.5)
North America	21 (47.7)	590 (46.1)	451 (35.4)	335 (28.6)	558 (33.0)	1955 (35.8)
South America	2 (4.5)	139 (10.9)	196 (15.4)	204 (17.4)	229 (17.7)	840 (15.4)
Rest of world	0	100 (7.8)	119 (9.3)	127 (10.8)	165 (9.8)	511 (9.4)
BMI, mean (S.D.), kg/m^2	28.7 (7.7)	29.1 (7.1)	28.3 (6.6)	27.9 (6.4)	27.4 (5.7)	28.1 (6.4)
No. of previous csDMARDs, mean (S.D.)	1.2 (0.5)	1.4 (0.7)	1.6 (0.8)	1.7 (0.9)	1.9 (1.1)	1.7 (0.9)
Use of oral glucocorticoids, *n* (%)	24 (54.5)	656 (51.3)	639 (50.2)	628 (53.5)	892 (52.7)	2839 (52.0)
Oral glucocorticoid dose, mean (S.D.), mg/day[b]	7.3 (2.5)	7.0 (3.1)	6.7 (3.0)	6.9 (4.6)	6.7 (5.3)	6.8 (4.2)
RF positive, *n* (%)	19 (59.4)	554 (64.4)	638 (75.3)	633 (80.5)	955 (81.6)	2779 (75.8)
CRP, mean (S.D.), mg/dl	2.3 (2.6)	2.0 (2.6)	1.9 (2.5)	2.1 (2.7)	1.9 (2.3)	2.0 (2.5)
HAQ-DI, mean (S.D.)	1.4 (0.7)	1.5 (0.6)	1.5 (0.6)	1.5 (0.6)	1.6 (0.6)	1.5 (0.6)
DAS28, mean (S.D.)	6.3 (1.1)	6.4 (1.1)	6.4 (1.1)	6.5 (1.0)	6.4 (1.1)	6.4 (1.1)
CDAI, mean (S.D.)	37.5 (13.4)	39.8 (13.7)	39.0 (13.9)	39.0 (13.3)	39.4 (13.6)	39.3 (13.6)

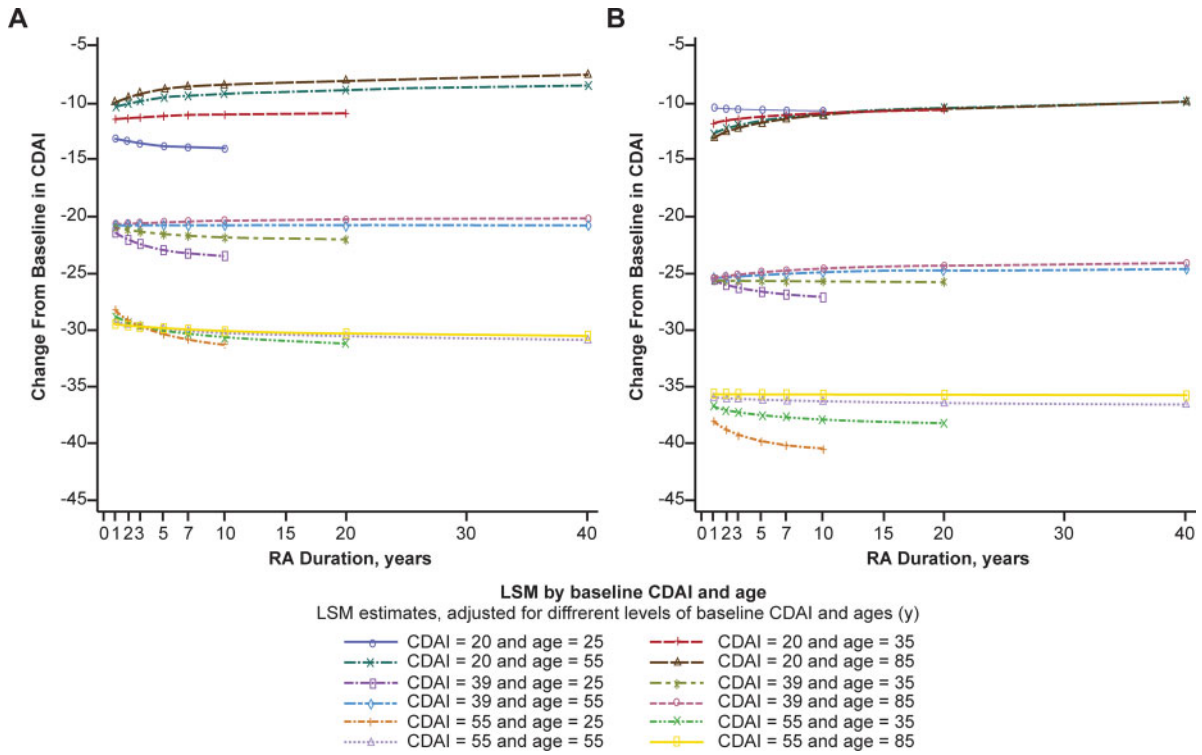
[a]RF positivity was not assessed in three studies (ROSE, ACT-STAR and ACT-SURE) and was only available in a minority of patients in ACT-RAY; HAQ-DI data were not assessed in two studies (ROSE and ACT-STAR); BMI was not assessed in one study (ACT-SURE). [b]In prednisone equivalents. CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic DMARD; DAS28: DAS based on 28 joints; HAQ-DI: HAQ–Disability Index.

Fig. 1 ANCOVA for estimated mean change in HAQ-DI from baseline to week 24



ANCOVA: analysis of covariance; HAQ-DI: HAQ–Disability Index; LSM: least squares mean. HAQ-DI data were not assessed in two studies (ROSE and ACT-STAR).

Fig. 2 ANCOVA for change in CDAI from baseline to week 24 according to age and region



(**A**) North America and (**B**) Europe, South America and rest of the world. ANCOVA: analysis of covariance; CDAI: Clinical Disease Activity Index; LSM: least squares mean.

remission of the adjusted model decreased by 15% for each additional 5 years of RA duration (odds ratio 0.85; 95% CI: 0.79, 0.91) (Table 4). Each additional 10 units of baseline CDAI score decreased the odds of achieving CDAI remission at week 24 by 22% (odds ratio 0.78; 95% CI: 0.71, 0.86) (Table 4). Among all variables tested, achievement of CDAI remission at week 24 in the adjusted model was influenced significantly, alone or in interaction terms, by baseline RA duration, CDAI, RAPID3, CRP levels, oral glucocorticoid use, number of previous csDMARDs, region, age, sex and body weight (Table 4).

Overall, 43% (2370/5462) of patients achieved ACR50 response by week 24. Doubling the duration of RA decreased the odds of achieving ACR50 response at week 24 by 9.2% (odds ratio 0.91; 95% CI: 0.87, 0.95). Among all variables tested, achievement of ACR50 response at week 24 in the adjusted model was influenced significantly, alone or in interaction terms, by baseline RA duration, CRP levels, region (North America *vs* Europe), sex and weight (Table 4).

Discussion

This pooled analysis of data from 5462 biologic-naïve patients with established RA who initiated tocilizumab i.v. or s.c., either as monotherapy or in combination with csDMARDs, in 12 phase 3 or 4 clinical trials, is the first of its kind. It determined the effects of disease duration and of other baseline factors on clinical efficacy and HAQ-DI outcomes in patients with RA initiating tocilizumab. The effect of disease duration and early treatment initiation on outcomes has been investigated in observational, registry and retrospective studies [1–3, 7, 10–12, 29–32], as well as in meta-analyses [6, 33], generally showing a statistically significantly negative effect of disease duration on outcomes with RA therapies. However, our pooled analysis in a large population of clinical trials is more robust. It provided a unique opportunity to investigate to what extent disease duration and other baseline factors of inflammation and disease burden influence clinical and patient-reported outcomes of tocilizumab treatment. Statistical tests among large samples might yield statistically significant *P*-values for very small, clinically not relevant effects; therefore, *P*-values alone should not be used as a basis for scientific or clinical conclusions [34, 35]. By quantifying effects in our analysis, we were able to put weakly predictive factors that were 'significant' according to *P*-values into relevant clinical context and perspective. This provided the clinically important insight that, although longer disease duration had a statistically significantly negative effect, in line with the literature, on efficacy outcomes following tocilizumab treatment, outcomes were not heavily influenced by disease duration among patients with

Table 3 ANCOVA results for changes from baseline to week 24 in HAQ-DI ($N = 5064$)[a] and CDAI ($N = 5462$)

	HAQ-DI	CDAI
	Estimate (95% CI), *p*	**Estimate (95% CI), *p***
Base Model		
BIC	8912.0	44 424.3
Explained variance[b]	0.95%	0.001%
RA duration[c]	0.05 (0.04, 0.07), $P < 0.0001$	0.17 (–0.18 to 0.53), $P = 0.3421$
Model with only baseline HAQ-DI and CDAI, respectively		
BIC	8177.9	42379.0
Explained variance[b]	14.97%	31.72%
Final model with RA duration and other predictors		
BIC	7810.0	41 268.9
Explained variance[b]	21.38%	35.38%
Main effects	*RA duration[c]* *Baseline HAQ-DI* *Baseline CRP* *Weight* *Age* *Sex* Region[d]	*RA duration[c]* Age *Baseline CDAI* Baseline CRP Baseline RAPID3 Oral glucocorticoid use *Number of previous csDMARDs* Region Sex *Weight*
Two-way interaction	*RA duration[c] and baseline HAQ-DI* *RA duration[c] and weight* *RA duration[c] and age* RA duration[c] and sex Age and sex *Baseline HAQ-DI and region*	*RA duration[c] and baseline CDAI* *RA duration[c] and oral glucocorticoid use* *RA duration[c] and number of previous csDMARDs* RA duration[c] and region *RA duration[c] and weight* Age and baseline CDAI Age and region *Age and sex* Baseline CDAI and region *Baseline CDAI and sex* *Baseline CRP and baseline RAPID3* Baseline CRP and oral glucocorticoid use *Baseline CRP and sex* Number of previous csDMARDs and region *Oral glucocorticoid use and region* Sex and oral glucocorticoid use *Weight and baseline CRP* Weight and number of previous csDMARDs
Three-way interaction	*RA duration[c] and age and sex*	Age and baseline CDAI and region *Baseline CRP and sex and oral glucocorticoid use*
Final model with RA duration as variable removed[e]		
BIC	7901.3	41 288.5
Explained variance[b]	19.7%	35.2%

Patients treated with any biologic before enrolment were excluded. Missing values for HAQ-DI and CDAI were imputed using the last available postbaseline value. Variables shown in italics are statistically significant ($P < 0.05$). [a]HAQ-DI data were not assessed in two studies (ROSE and ACT-STAR). [b]Assessed using residual variance method. [c]Transformed by natural logarithm. [d]Region is the location category of patients (North America, South America, Europe and rest of world). [e]Model with RA duration and all interaction terms with RA duration removed. ANCOVA: analysis of covariance;
BIC: Bayes Information Criterion; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic DMARD;
HAQ-DI: HAQ–Disability Index; RAPID3: Routine Assessment of Patient Index Data 3.

established RA. In our study, the odds ratios of achieving efficacy outcomes decreased slightly with RA of longer duration. In 4992 patients from a Norwegian registry treated with csDMARDs, relatively longer disease duration (>6 *vs* ≤6 months) was shown to decrease the odds of achieving CDAI remission by ∼20% [5]. In 3179

Table 4 Logistic regression analysis of CDAI remission and ACR50 response at week 24 ($N = 5462$)

Adjusted model for CDAI remission	Odds ratio (95% CI)[a]
RA duration (per 5 years)	0.85 (0.79, 0.91)
Baseline CDAI (per 10 score units)	0.78 (0.71, 0.86)
Baseline CRP (per mg/dl)	1.07 (1.04, 1.09)
Baseline RAPID3 (per unit score)	0.90 (0.85, 0.95)
Region	
North America *vs* Europe	0.65 (0.46, 0.91)
South America *vs* Europe	0.64 (0.47, 0.89)
Rest of world *vs* Europe	1.01 (0.77, 1.35)
Age (per decade)	1.04 (0.98, 1.10)
Sex (male *vs* female)	1.17 (1.05, 1.30)
Weight (per 10 kg)	0.92 (0.89, 0.96)
No. of previous csDMARDs	0.99 (0.87, 1.12)
Baseline oral glucocorticoids (yes *vs* no)	0.94 (0.75, 1.17)
Adjusted model for ACR50 response	**Odds ratio (95% CI)[b]**
RA duration (doubling)[c]	0.91 (0.87, 0.95)
Baseline DAS28 (per unit score)	0.99 (0.92, 1.05)
Baseline CRP (per mg/dl)	1.06 (1.04, 1.08)
Age (per decade)	0.96 (0.92, 1.01)
Sex (male *vs* female)	1.21 (1.06, 1.38)
Region	
North America *vs* Europe	0.60 (0.53, 0.68)
Rest of world[d] *vs* Europe	1.07 (0.80, 1.42)
Weight (per 10 kg)	0.93 (0.89, 0.97)
Previous csDMARDs, *n*	0.94 (0.85, 1.05)
Baseline oral glucocorticoids (yes *vs* no)	0.95 (0.86, 1.07)

Patients treated with any biologic before enrolment were excluded. Missing week 24 values for CDAI remission and ACR50 were imputed as no CDAI remission and no ACR50 response, respectively. The adjusted logistic regression model for CDAI remission included RA duration as a fixed predictor and additional fixed baseline covariates of CDAI, sex, region, age, weight, number of previous csDMARDs, oral glucocorticoid use, CRP, RAPID3 and two-way interactions of RA duration with sex, age and number of previous csDMARDs, age with sex, sex with glucocorticoid use and glucocorticoid use with number of previous csDMARDs. Study was included as a random effect. The adjusted logistic regression model for ACR50 response included RA duration as a fixed predictor and additional fixed baseline covariates of DAS28, sex, region, age, weight, number of previous csDMARDs, oral glucocorticoid use, CRP and two-way interactions of RA duration with sex, weight and number of previous csDMARDs, age with sex, glucocorticoid use with number of previous csDMARDs and region with weight. Study was included as a random effect. [a]Quasi-AIC, 3628; Harrell's C, 0.68. [b]Quasi-AIC, 7238; Harrell's C, 0.62. [c]Transformed by natural logarithm. [d]Rest of world includes South America. ACR50: ≥50% improvement in ACR criteria; AIC: Akaike information criterion; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic DMARD; DAS28: DAS at 28 joints; RAPID3: Routine Assessment of Patient Index Data 3.

patients from the Consortium of Rheumatology Researchers of North America registry initiating TNF inhibitors, the odds of achieving CDAI remission decreased by 12% for every 5-year increase in disease duration [1]. A relatively short disease duration (<5 years) was shown to increase the odds of achieving Boolean remission by more than 2-fold in 123 patients with RA treated with tocilizumab, compared with a longer disease duration [2]. These modest decreases in remission rates of 12 and 20% reported with longer disease duration are similar to our result of 15%. The 2-fold (100%) increase for Boolean remission reported with shorter disease duration was a result from a small study in Japan [2].

It might be speculated that in multivariable analyses such as those performed in the current study, the effect of longer disease duration in patients with established RA would negate the effect of the number of csDMARDs used because the two are correlated. However, as has been shown in other studies [32], the number of csDMARDs used had an independent effect on treatment outcomes, likely reflecting the fact that the number of csDMARDs is a surrogate marker of difficult-to-treat RA [36].

Outcomes at week 24 were more heavily influenced by baseline values of HAQ-DI and CDAI in our analysis, showing that greater disability and higher disease activity at baseline were associated with larger changes in

week 24 outcomes. Our findings contrast with those of other studies which showed that higher levels of certain disease activity measures at baseline were negatively associated with treatment outcomes in patients with RA [31]. A possible explanation could be that all studies, except one, included in our analysis enrolled biologic-naïve patients with inadequate response to MTX or other csDMARDs and that therefore, in our study population, high baseline values are indicative of patients with greater potential to achieve an improvement in disease activity on their first biologic.

Limitations of study

Several study limitations should be considered when drawing conclusions from these results. For most but not all of the included studies, RA disease duration of $\geq$6 months was an eligibility criterion; therefore, the findings of these analyses may not precisely characterize shorter disease durations. Although heterogeneity in our study was minimized by limiting the analyses primarily to patients who had received similar treatment (MTX/csDMARDs-IR with tocilizumab as first-line biologic), the pooled patient population might not have been completely homogeneous with respect to disease state. This might have contributed to unexplained variation in outcomes. Because csDMARD-naïve patients were excluded to minimize heterogeneity, the findings and conclusions of this study are most relevant primarily to csDMARDs-IR patients with established RA. In addition, given that our analyses included only patients with established RA from tocilizumab groups of clinical trials and not comparator groups, the findings may not be generalizable to other therapies. Although several potential predictors were considered in the models, it is possible that some variability might be predicted by other factors that were not assessed in most of the trials (e.g. other proteins, peptides, inflammatory markers, subjective factors). Not all variables had been assessed in the 12 trials. RF status was not included in the models because it was not available in three studies and only available in a minority of patients in another study. However, in the eight studies that consistently assessed RF positivity, it showed a modest interaction with RA duration on CDAI and HAQ change models, reducing the effect of disease duration even more. Finally, the models used were those that best fitted the data and were not necessarily the models that would generalize precisely across other data sets in terms of variance explained or of clinical practice.

In conclusion, tocilizumab treatment outcomes from clinical trials were not heavily influenced by disease duration, either alone or in combination with other baseline characteristics, in patients with established RA. Rather, baseline values of outcome variables were stronger predictors of outcome variables. Additional studies may be warranted to further elucidate the potential of other patient and disease factors to predict responses to tocilizumab and other medications.

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Data availability statement

Qualified researchers may request access to data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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