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Original article

Female reproductive status and exogenous sex hormone use in rheumatoid arthritis patients treated with tocilizumab and csDMARDs

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Abstract

Objectives. Sex is well known to influence risk, severity and treatment outcomes of RA, although the underlying causes are uncertain. The aim of this research was to examine whether factors influencing female sex hormones (reproductive status and exogenous sex hormone use) are associated with the efficacy of DMARDs.

Methods. Individual participant data were pooled from five phase 3 clinical trials where RA patients were treated with tocilizumab and/or conventional synthetic DMARDs. The primary outcome was the time to first remission according to the Simplified Disease Activity Index. The relationship between menopausal status or use of exogenous sex hormones and the time of first remission was assessed via Cox proportional analysis. Analysed data included sex, baseline menopausal status (premenopausal, perimenopausal, early postmenopausal and postmenopausal), participant age, body mass index, race, number of previous DMARDs and baseline disease activity.

Results. Analysis included 4474 female patients, of whom 2817 (62.9%) were postmenopausal, 202 (4.5%) were early postmenopausal, 1021 (22.8%) were premenopausal and 414 (9.2%) were perimenopausal. Of these, 221 (7.8%), 13 (6.4%), 255 (25%) and 47 (11.4%), respectively, were taking exogenous sex hormones. In the pooled analysis, perimenopausal status was associated with reduced remission compared with premenopausal status [adjusted HR 0.78 (95% CI 0.61, 0.99)]. Sex hormone use was associated with significantly higher remission [adjusted HR 1.20 (95% CI 1.01, 1.43)].

Conclusion. Perimenopausal women were less likely to achieve remission compared with premenopausal RA patients. The use of exogenous sex hormones appeared to be associated with more frequent remission in female RA patients, particularly those who were perimenopausal and early postmenopausal, although further research is required to confirm and identify the drivers for this observation and how it interacts with menopausal status.

CLINICAL SCIENCE

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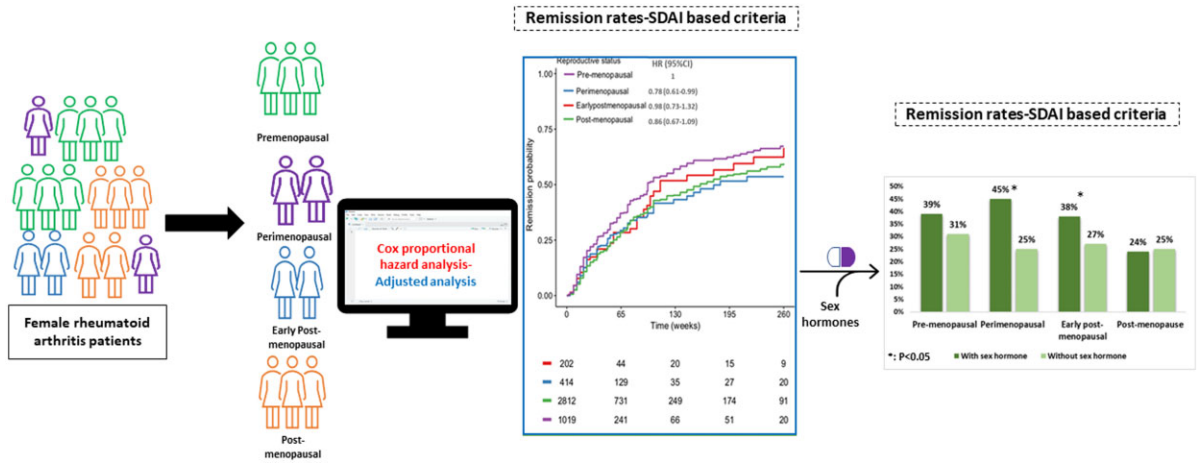
Graphical Abstract



Key words: RA, remission, perimenopausal, early post-menopausal, exogenous sex hormone, tocilizumab, csDMARDs

Rheumatology key messages

- Perimenopausal women with RA were less likely to achieve remission compared to premenopausal women.
- Perimenopausal and early postmenopausal RA patients taking exogenous sex hormones had an improved likelihood of remission.
- Exogenous sex hormone use was not associated with remission likelihood in postmenopausal RA patients.

Introduction

RA is an autoimmune inflammatory disease that is characterized by articular and extra-articular complications that are associated with permanent disability and increased mortality [1]. Two broad strategies have been recommended by the ACR and EULAR for the treatment of RA patients: monotherapy with conventional synthetic DMARDs (csDMARDs; i.e. MTX, HCQ, SSZ or LEF) or combination therapy that includes two or more csDMARDs [2, 3]. Whatever initial therapy is used, a treat-to-target approach is advocated, whereby doses are increased and/or DMARDs added until the desired level of disease activity is achieved [4]. The aim of this treatment is generally to achieve remission as soon as possible [5]. The 2011 ACR/EULAR guidelines provide two definitions of remission for use in clinical trials. One is a Boolean-based definition that defines remission as a disease state where both swollen joint count (SJC) and tender joint count (TJC) using 28-joint counts are $\leq$1, CRP is $\leq$1 mg/dl and patient global assessment of disease is $\leq$1 cm (on a 0–10 cm visual analogue scale). The other definition is based on the Simplified Disease Activity Index (SDAI), which is reported using a continuous scale and incorporates SJC, TJC, CRP and patient and physician global assessment of disease activity, whereby remission is defined as a score of $\leq$3.3 [6]. Other indices that have been widely used in defining remission are the Clinical Disease Activity Index (CDAI $\leq$2.8), where the CDAI is identical to the SDAI except CRP is not included, and the 28-joint DAS with ESR (DAS28-ESR $\leq$2.6), which is calculated using SJC, TJC, patient global assessment and ESR [6].

RA is more prevalent in females than males with a 4 female:1 male ratio at younger ages ($<$50 years old) and a 2:1 ratio at older ages ($>$60 years) [7]. Compared with males, females tend to have higher DASs, worse prognosis [8–10] and are less likely to achieve remission [11, 12]. Although the cause of these sex-based differences is unknown, they indicate a potential impact of sex-related factors (i.e. reproductive status and sex hormones) on RA treatment outcome.

Premenopausal female RA patients have reported greater functional improvement (measured by the HAQ) in response to DMARD treatment compared with postmenopausal women [13, 14]. The peak age of onset of RA among females is 45–55 years, corresponding with the perimenopausal period [15, 16], which is associated

with physiological and hormonal changes, including a decline in systemic oestrogen concentrations. Furthermore, at the onset of menopause there is an increase in pro-inflammatory cytokines such as IL-6 and TNF-α [17–19] that are the target of highly effective pharmacological agents [i.e. anti-IL-6 agents such as tocilizumab (TCZ) and anti-TNF agents]. Early menopause (i.e. <45 years) increases the risk of developing RA [20]. Pregnancy is also associated with substantial changes in systemic hormone exposure, and throughout pregnancy disease activity decreases in ∼50% of women, but conversely it increases in 90% of women during the post-partum period [21–23].

Exogenous sex hormone use has been hypothesized as having a protective role in RA, but findings from various studies are inconsistent [24]. While exogenous oestrogen may not reduce the risk of RA, it may improve treatment outcomes [24]. Sex hormone replacement in postmenopausal women with RA has been found to have beneficial effects, including improved bone mineral density [25, 26] and decreased inflammatory mediators and disease activity [26].

Associations have been observed between gender, menopausal status and exogenous sex steroid exposure with RA onset and prognosis, and there is a potential role of inflammatory cytokines that are directly affected by commonly used DMARDs. As such, the aim of this study was to use data from five phase 3 randomized controlled trials (RCTs) to investigate the association between female reproductive status and the use of exogenous sex hormones with the likelihood of achieving remission in RA patients after initiation of csDMARDs and/or TCZ.

Patients and methods

Patient population

Individual participant data were pooled from five phase 3 RCTs {LITHE [27] (clinicaltrials.gov identifier number NCT00106535), AMBITION [28] (NCT00109408), TOWARD [29] (NCT00106574), FUNCTION [30] (NCT01007435) and SUMMACTA [31] (NCT01194414)}. In these trials, patients with moderately to severely active RA received either csDMARDs or TCZ (4 or 8 mg/kg once every 4 weeks, either as monotherapy or in combination with csDMARDs, mainly MTX). All studies included patients with inadequate response to one or more DMARD, except FUNCTION, which included patients who were MTX and biological DMARD naïve. Background use of systemic corticosteroids or NSAIDs were permitted in all trials.

Data were accessed according to Hoffmann-La Roche policy and have been made available through Vivli (www.vivli.org). All studies were conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline and the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrolment.

Female reproductive status subgroups and exogenous sex hormone use

Four baseline reproductive status groups were derived from available data on menopausal status (pre- or post-) and age (<45 years or ≥45 years) (Fig. 1). The method used to determine menopausal status was not stated for each included trial and groups were defined as premenopausal (premenopausal with an age <45 years), perimenopausal (premenopausal with an age ≥45 years [32]), early postmenopausal (postmenopausal with an age <45 years [33]) and postmenopausal (postmenopausal with an age ≥45 years).

Data on concomitant use of exogenous sex hormones (any dose or route of administration of oestrogen or/and progesterone) was also available at baseline—this was mainly hormone replacement therapy and contraception.

Predictors and outcomes

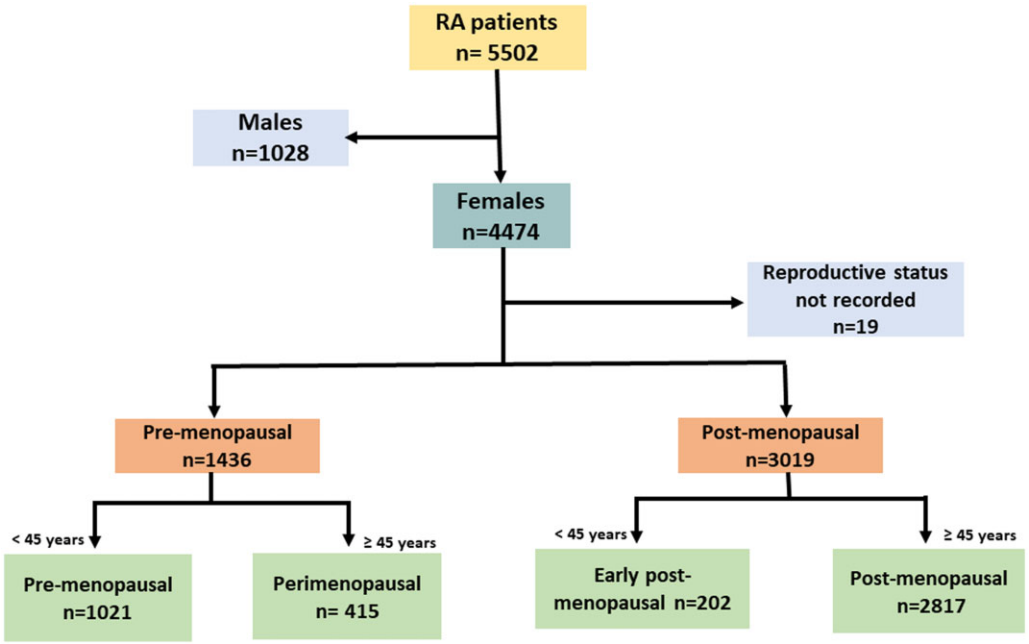
Baseline demographic, clinical and disease characteristics were available for analysis. Disease activity measures (SDAI, CDAI and DAS28-ESR and their individual components) were collected at baseline (i.e. at the initiation of RA therapy) and followed over the duration of the trials. The primary outcome was the time to first RA disease remission according to the SDAI [6]. The time to first RA disease remission according to the CDAI and DAS28-ESR were secondary outcomes [6]. Exploratory outcomes were the time to achieve remission for the individual components of SDAI, CDAI and DAS28-ESR, which were prespecified as TJC ≤1, SJC ≤1, CRP ≤1 mg/dl [6], which corresponds approximately to ESR <30 mm/h (i.e. CRP <1 mg/dl) among female patients [6, 34] and physician and patient assessment of disease activity <1 on a 10 cm visual analogue scale [6]. Patients who had not achieved remission were censored at the last known date of follow-up or at the recorded date of death. Female reproductive status and exogenous sex hormone use at baseline were assessed as the primary predictors of remission.

Statistical analysis

The relationship between female reproductive status and exogenous sex hormone use with SDAI, CDAI or DAS28-ESR remission likelihood was assessed via Cox proportional hazards analysis. Analyses of the association of reproductive status with the exploratory individual components of the SDAI, CDAI and DAS28-ESR (i.e. TJC, SJC, CRP, ESR and physician and patient assessments of disease activity) were conducted. Exploration of the association between exogenous sex hormone use according to reproductive status subgroup with remission likelihood according to SDAI, CDAI and DAS28-ESR were also assessed.

All analyses were adjusted for potentially confounding factors (e.g. BMI, race, RA disease duration, number of previous DMARDs, exogenous vitamin D use, use of systemic corticosteroids and baseline RF and ACPA status). Associations were reported as hazard ratios (HRs) with

Fig. 1 Patients included in the analysis



95% CIs. Statistical significance was set at $P < 0.05$. Complete case analyses were conducted. All analyses were stratified by study and treatment arm. The heterogeneity of the association of female reproductive status and exogenous sex hormone use with remission according to treatment and study was assessed using a treatment × biomarker interaction term in the Cox proportional regression model. Kaplan–Meier analysis was used for plotting and estimating remission probabilities. Baseline patient characteristics were summarized by calculating the frequency (%) for binary variables and the median [interquartile range (IQR)] for continuous variables. All analyses were conducted using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient demographics and baseline characteristics

Baseline and demographic characteristics by study, reproductive status and exogenous sex hormone use are summarized in Supplementary Tables S1–S3, respectively (available at *Rheumatology* online). The analysis included data from 4474 female participants, of which 3347 (75%) received TCZ ± csDMARDs and 1127 (25%) received csDMARDs alone. A total of 1021 (23%) participants were premenopausal and 415 (9%) were perimenopausal. Of the premenopausal participants, 255 (25%) were using exogenous sex hormones and 47 (11%) of the perimenopausal participants were using exogenous sex hormones. A total of 2817 (63%) of the participants were postmenopausal and 202 (5%) were early postmenopausal, of whom 221 (8%) and 13 (6.4%) were using exogenous sex hormones, respectively. SDAI, CDAI and DAS28-ESR at baseline were missing for 42, 40 and 57 patients, respectively, and for the SDAI, CDAI and DAS28-ESR adjusted analysis, 166 (3.7%), 135 (3%) and 154 (3.4%) patients, respectively, were excluded due to missing adjustment data.

The 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 female reproductive status and remission

Adjusted analysis indicated that reproductive status was not associated with SDAI remission ($P = 0.234$), however, the association was significant with remission defined by CDAI ($P = 0.018$) and DAS28-ESR ($P < 0.001$) (Table 1). A primary driver of the associations was the consistent relationship between perimenopausal status and reduced remission {defined by SDAI [HR 0.78 (95% CI 0.61, 0.99)], CDAI [0.69 (0.55, 0.87)] and DAS28-ESR [0.68 (0.57, 0.81)]} compared with the premenopausal group. Further, the postmenopausal group also trended towards reduced remission according to the SDAI [HR 0.86 (95% CI 0.67, 1.09)], CDAI [0.82 (0.65, 1.02)] and DA28-ESR [0.84 (0.70, 0.99)] compared with the premenopausal group. Kaplan–Meier estimates of remission rate according to reproductive status are presented in Fig. 2. These Kaplan–Meier curves demonstrate that, immediately after initiation of therapy, remission appears higher in premenopausal compared with early postmenopausal women, but over time and after consideration of other variables,

TABLE 1 Adjusted pooled cohort analysis of the association between female reproductive status and remission

Pooled cohort	SDAI remission			CDAI remission			DAS28-ESR		
	Events/patients[a], *n/n* (%)	HR (95% CI)	*P*-value	Events/patients[a], *n/n* (%)	HR (95% CI)	*P*-value	Events/patients[a], *n/n* (%)	HR (95% CI)	*P*-value
Female reproductive status			0.234			0.018			<0.001
Premenopausal	322/989 (33)	1		401/1002 (40)	1		630/998 (64)	1	
Perimenopausal	112/404 (28)	0.78 (0.61, 0.99)		121/406 (30)	0.69 (0.55, 0.87)		215/402 (53)	0.68 (0.57, 0.81)	
Early postmenopausal	54/196 (28)	0.98 (0.73, 1.32)		63/198 (32)	0.93 (0.71, 1.23)		94/197 (48)	0.81 (0.64, 1.01)	
Postmenopausal	689/2719 (25)	0.86 (0.67, 1.09)		782/2733 (29)	0.82 (0.65, 1.02)		1407/2723 (52)	0.84 (0.70, 0.99)	

Adjustment variables: BMI, age, race, RA disease duration, sex hormone use, systemic corticosteroids use, RF, ACPA, exogenous vitamin D use. [a]Median follow-up cross included studies ranging between 24 and 260 weeks.

no difference was apparent (Table 1). Supplementary Table S4, available at *Rheumatology* online, presents univariable Cox regression analyses.

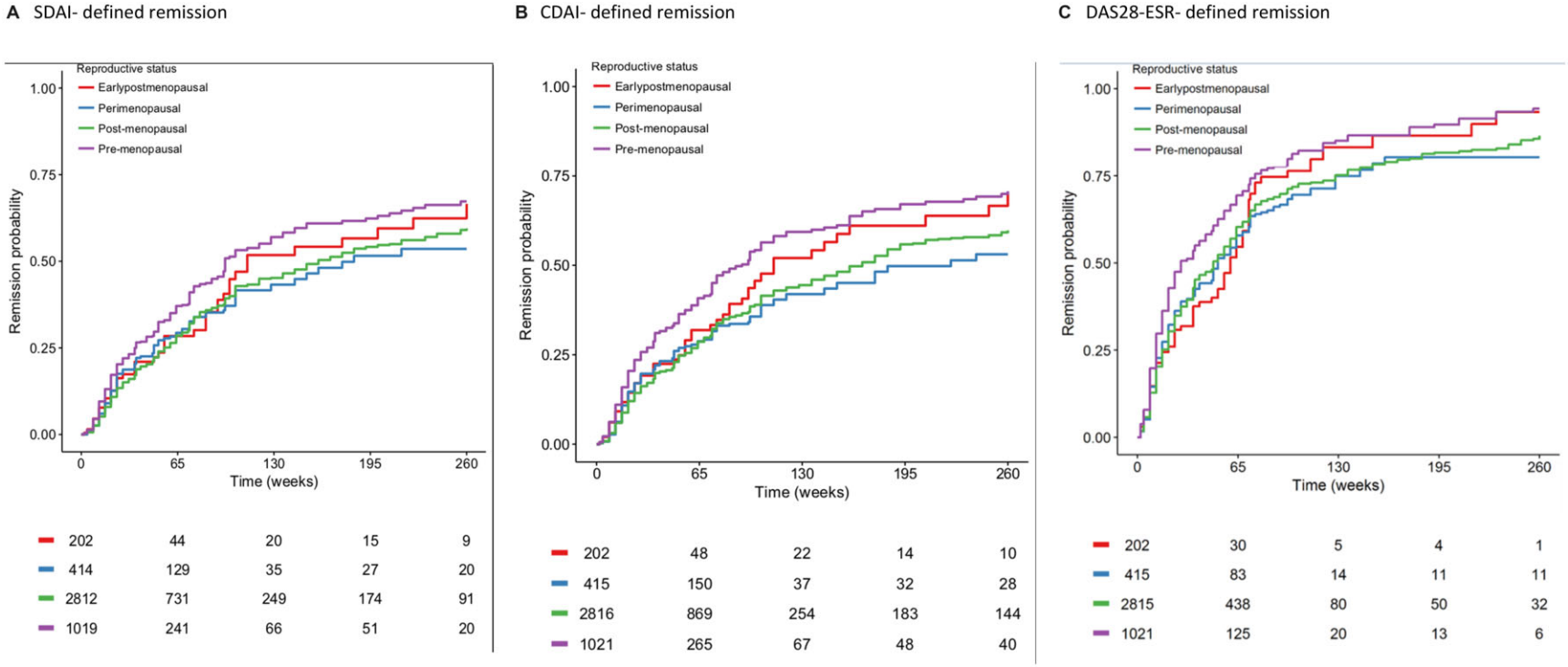
No significant heterogeneity between reproductive status and remission was observed between studies ($P > 0.05$) (Supplementary Table S5, available at *Rheumatology* online). The test for interaction between female reproductive status subgroups and treatment allocation (i.e. TCZ ± csDMARDs *vs* csDMARDs alone) was not significant using SDAI-, CDAI- and DAS28-ESR-defined remission (P for interaction > 0.1; Supplementary Table S6, available at *Rheumatology* online). Exploratory analysis indicated that perimenopausal women were more likely to have CRP <1 compared with premenopausal women, whereas they were less likely to have a TJC <1 and physician assessment of disease activity <1 cm (Supplementary Table S7, available at *Rheumatology* online).

Association between exogenous sex hormone use and remission

On adjusted analysis, female participants who were taking exogenous sex hormones were more likely to achieve remission according to the SDAI [HR 1.20 (95% CI 1.01, 1.43), $P = 0.038$] and DAS28-ESR [HR 1.17 (95% CI 1.03, 1.32), $P = 0.014$], but there was no statistically significant association with remission according to the CDAI [HR 1.09 (95% CI 0.93, 1.29), $P = 0.297$] (Table 2). Further, significant associations were observed between exogenous sex hormone use and outcomes based on ESR and patient and physician assessment of disease activity (Supplementary Table S8, available at *Rheumatology* online). Supplementary Table S9, available at *Rheumatology* online, presents univariable Cox regression analyses. Kaplan–Meier estimates of remission rate according to exogenous sex hormone use are presented in Fig. 3. No significant heterogeneity between exogenous sex hormone use and remission was observed between studies or treatment arms (Supplementary Tables S10 and S11, available at *Rheumatology* online).

On exploratory analysis of the perimenopausal subgroup, those taking exogenous sex hormones were more likely to achieve SDAI- and CDAI-defined remission [SDAI: HR 2.18 (95% CI 1.27, 3.72), $P = 0.004$; CDAI: HR 1.86 (95% CI 1.09, 3.15), $P = 0.022$] (Table 2). Further, in the early postmenopausal subgroup, SDAI- and DAS28-ESR-defined remission was more likely in women who were taking exogenous sex hormones [SDAI: HR 4.33 (95% CI 1.36, 13.8), $P = 0.013$; DAS28-ESR: HR 2.96 (95% CI 1.10, 6.55), $P = 0.030$; Table 2]. No significant differences in remission likelihood were observed in the premenopausal group and there was a significant association with DAS28-ESR-defined remission and the use of exogenous sex steroids in postmenopausal women [HR 1.28 (95% CI 1.05, 1.55), $P = 0.014$; Table 2, Fig. 4]. Supplementary Tables S12 and S13, available at *Rheumatology* online, present univariable and adjusted Cox regression analyses, respectively.

FIG. 2 Kaplan–Meier estimates of the proportion of RA patients achieving remission by female reproductive status



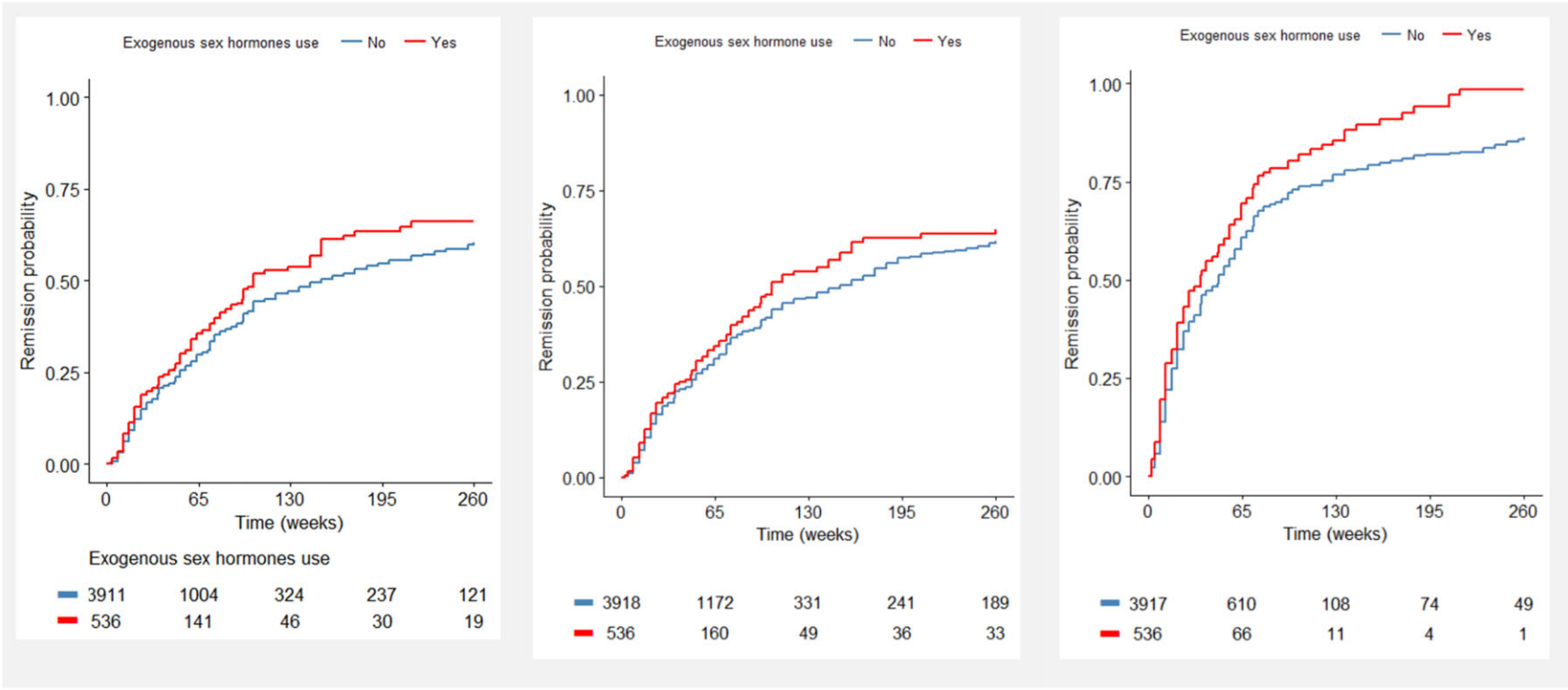
Kaplan–Meier estimates of the proportion of RA patients achieving remission by female reproductive status in the pooled cohort using **(A)** SDAI-, **(B)** CDAI- and **(C)** DAS28-defined remission. The numbers underneath the Kaplan–Meier plots indicate the absolute number of patients at risk by time.

Table 2 Adjusted analysis of the association between exogenous sex hormone use and remission in the pooled cohort

Pooled cohort	SDAI remission			CDAI remission			DAS28-ESR		
	Events/patients, *n/n* (%)	HR (95% CI)	*P*-value	Events/patients, *n/n* (%)	HR (95% CI)	*P*-value	Events/patients, *n/n* (%)	HR (95% CI)	*P*-value
Exogenous sex hormone use									
No	1004/3787 (27)	1	0.038	1178/3814 (31)	1	0.297	2022/3797 (53)	1	0.014
Yes	173/521 (33)	1.20 (1.01, 1.43)		189/525 (36)	1.09 (0.93, 1.29)		324/523 (62)	1.17 (1.03, 1.32)	
Exogenous sex hormone use (post-menopausal)									
No	638 (25)	1	0.122	724 (29)	1	0.265	1292 (51)	1	0.014
Yes	51 (24)	1.25 (0.94, 1.65)		58 (27)	1.17 (0.89, 1.54)		115 (54)	1.28 (1.05, 1.55)	
Exogenous sex hormone use (early post-menopause)									
No	49 (27)	1	0.013	58 (31)	1	0.067	87 (47)	1	0.03
Yes	5 (38)	4.33 (1.36, 13.8)		5 (38)	2.77 (0.93, 8.25)		7 (58)	2.96 (1.10, 6.55)	
Exogenous sex hormone use (pre-menopause)									
No	226 (31)	1	0.571	295 (39)	1	0.391	459 (61)	1	0.600
Yes	96 (39)	1.08 (0.84, 1.39)		106 (42)	1.08 (0.91, 1.28)		171 (68)	1.05 (0.87, 1.27)	
Exogenous sex hormone use (perimenopause)									
No	91 (25	1	0.004	101 (28)	1	0.022	184 (52)	1	0.120
Yes	21 (45)	2.18 (1.27, 3.72)		20 (43)	1.86 (1.09, 3.15)		31 (66)	1.41 (0.91, 2.17)	

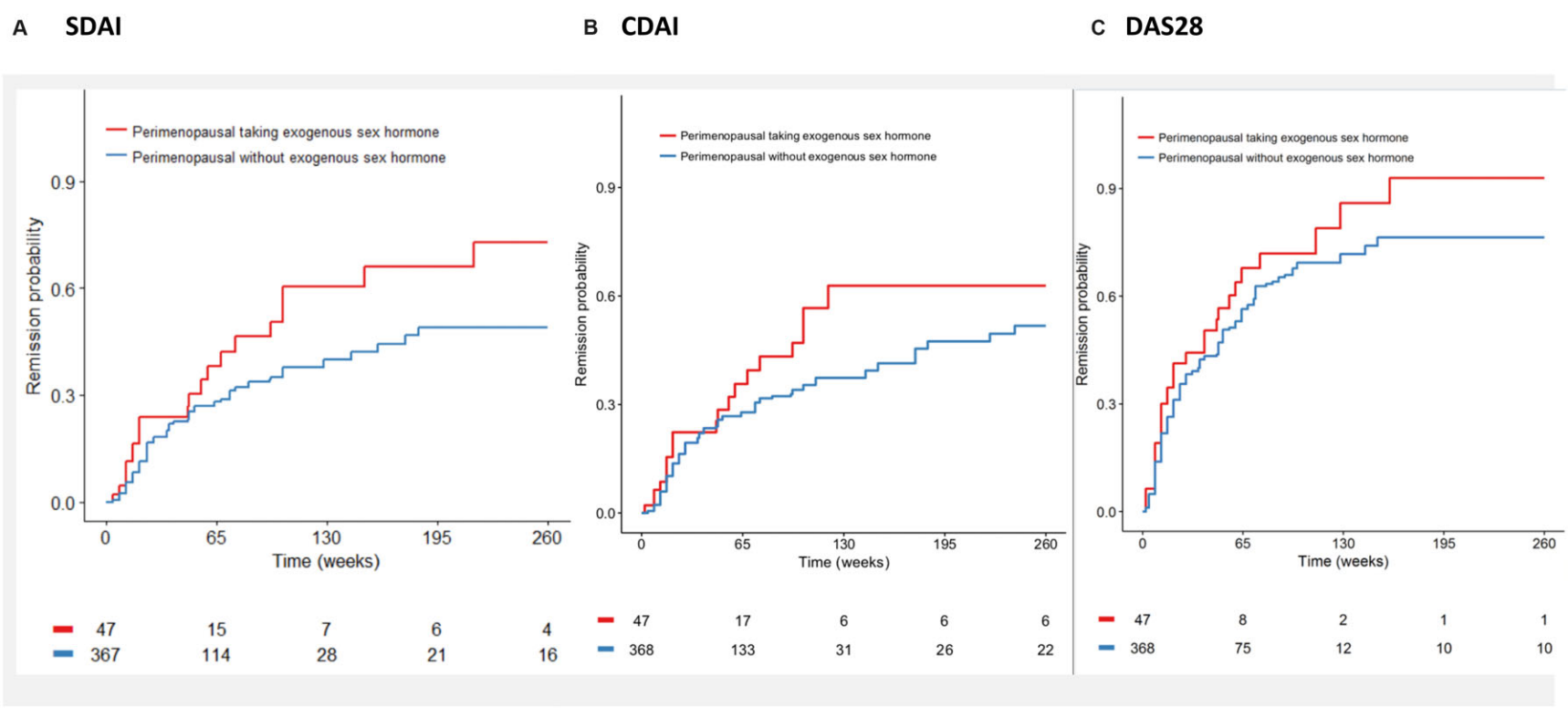
Adjustment variables: BMI, age, race, female reproductive status, RA disease duration, use of systemic corticosteroids, RF, ACPA, exogenous vitamin D use, baseline disease activity (SDAI, CDAI, DAS28-ESR scores) and number of previous DMARDs.

FIG. 3 Kaplan–Meier estimates of the proportion of female patients achieving remission by exogenous sex hormone use



Kaplan–Meier estimates of the crude proportion of RA patients achieving remission by exogenous sex hormone use in the pooled female cohort using **(A)** SDAI-, **(B)** CDAI- and **(C)** DAS28-defined remission. The numbers underneath the Kaplan–Meier plots indicate the absolute number of patients at risk by time.

FIG. 4 Kaplan–Meier estimates of the proportion of perimenopausal female patients achieving remission by sex hormone use



Kaplan–Meier estimates of the proportion of RA patients achieving remission by exogenous sex hormone use in the pooled female cohort using **(A)** SDAI-, **(B)** CDAI- and **(C)** DAS28-defined remission. The numbers underneath the Kaplan–Meier plots indicate the absolute number of patients at risk by time.

Discussion

Using data from five large independent RCTs investigating the effect of treatment with TCZ and/or csDMARDs in RA, perimenopausal women were less likely to achieve remission compared with premenopausal women. The use of exogenous sex hormones was associated with an increased likelihood of remission, with the impact most apparent in perimenopausal and early postmenopausal women, such that the lower remission likelihood in perimenopausal women appeared to be reversed by the use of exogenous sex hormones.

Several factors could explain why perimenopausal women are less likely than premenopausal women to achieve remission. First, the perimenopausal period, which is also known as transition menopause, is associated with hormonal fluctuations and deprivation, which has been associated with autoimmune disease provocation [35]. Second, since patients of the same age could have different reproductive status and hormone profiles, there may be an interaction between age and female reproductive status and RA prognosis and treatment outcomes. Thus both age and exposure to endogenous sex hormones may independently predict response to DMARDs.

In addition, females at menopause generally have more musculoskeletal pain [36], depression [37] and reduced quality of life [37]. These factors may also affect how health status is reported, which could influence the more subjective components of disease activity measures, such as TJC and patient and physician assessment of disease activity. Exploratory analyses were performed with each individual disease activity measure and perimenopausal and early postmenopausal women were less likely to achieve remission according to TJC $\leq$1 and physician assessment of disease activity $\leq$1/10 compared with premenopausal women, but no effect was apparent with patient assessment of disease activity. When considering more objective measures such as SJC, CRP and ESR, perimenopausal and postmenopausal women were more likely to have CRP $\leq$1 mg/dl compared with premenopausal women, but no difference was observed for ESR and SJC. The association with CRP could be explained in that women at menopause generally have higher plasma concentrations of IL-6, which is known to stimulate CRP production [38] and use of the IL-6 inhibitor TCZ is associated with reduced CRP [39]. These results suggest that the differences in outcomes between different female reproductive status groups appear to be more subjective rather than biological. However, these results are of great clinical usefulness as they suggest that women within the perimenopausal period need more support and closer disease monitoring.

Previous studies have reported an increase in IL-6 secretion at menopause [17, 18], so if this is driving disease activity, a better outcome may be expected from TCZ compared with csDMARDs among postmenopausal women. Alternatively, since IL-6 is elevated, more TCZ may be needed to inhibit it and therefore remission may be less likely in postmenopausal women treated with normal TCZ doses. However, in this study, remission in postmenopausal women was decreased regardless of the type of DMARD used.

The present study identified that the use of exogenous sex hormones was an independent predictor of remission. This is consistent with a small study demonstrating that hormonal replacement therapy was associated with lower DAS28 among postmenopausal women with established RA who were treated with csDMARDs [26]. However, in this study we investigated the association in more depth and using three different disease activity measures. Remission defined by SDAI and DAS28-ESR (but not CDAI) was more likely in users of exogenous sex hormones, suggesting a potential mechanistic role involving inflammatory mediators. Upon further examination of the individual disease activity markers, remission according to ESR was more likely in those who were taking exogenous sex hormones, but there was a trend for it to be less likely according to CRP. While there was no association with TJC and SJC, remission according to physician global assessment and patient global assessment were more likely in users of exogenous sex hormones, suggesting that while inflammatory mediators may well be involved in driving remission in individuals using exogenous sex hormones, other factors are also likely to contribute to the overall effect. For example, a significant association between exogenous sex hormone use and Boolean definitions of remission according to ESR and patient and physician assessment of disease activity were observed, while there was no association with TJC and SJC. Exogenous sex hormone use such as hormone replacement therapy could non-specifically improve subjective disease activity measures (patient and physician assessment of disease activity) without impacting underlying inflammatory processes. However, previous studies reported an increase in ESR with increasing age [40–42], and hormonal changes at menopause have been proposed to cause this phenomenon [41, 42], so exogenous sex hormones may also reduce inflammation, as measured by ESR, thus contributing to improved outcomes in RA patients with exogenous sex hormone use.

It is particularly noteworthy that the negative association between the perimenopausal state and remission was reversed by the concomitant use of exogenous sex hormones, which approximately doubled the likelihood of achieving remission in perimenopausal women. This may be due to improved stability of the hormonal profile in perimenopausal women. Given that the use of long-term hormone replacement therapy is not routinely advised due to safety-related issues [43], it is unclear if a short course of exogenous sex hormones delays rather than prevents a period of poor outcomes in perimenopausal women. Given that perimenopause is a transition period, further investigation of the association between exogenous sex hormone use and overall outcome in these patients is warranted.

The large number of patients included in this analysis is a strength of this study, as it allowed for a relatively high-powered analysis with adjustment for a number of potential confounders. The flexibility to conduct subanalyses according to female reproductive status is also a strength. Additionally, using three disease measures (SDAI, CDAI and DAS28-ESR) to investigate the consistency of our findings is another strength that increases the robustness of the findings.

The main limitation of this study is that the included clinical trials were not specifically designed to address the association between female reproductive status, exogenous sex hormone use and remission and therefore information regarding the dosage and duration of exogenous sex hormones use, age at menopause, menopausal classification criteria (i.e. hormonal, surgical) and the length of reproductive life is lacking, leading to an inability to determine whether changes in some or all of these variables might lead to a different response. Furthermore, the method used to determine menopause was not stated for each included trial. A limitation of this analysis is that there might be other confounders that were not available in the clinical trial data, such as smoking status and age at menopause, that were not included in the analysis. Another limitation is that, despite the large number of patients, there were comparatively few who used exogenous sex hormones, especially after the participant group was split into four reproductive subgroups. There may be difficulty in generalizing results obtained from RCTs, as the patients included in the RCTs may be quite different from those treated in clinical practice. Thus additional validation studies investigating female reproductive status and exogenous sex hormone use among a broader group of RA patients with longer follow-up duration is required.

Overall, our results suggest that the rate of RA remission was influenced by female reproductive status and that perimenopausal women were least likely to achieve remission. Furthermore, our analysis suggests that exogenous sex hormone use was independently associated with higher remission rate, particularly in perimenopausal and early postmenopausal women, but further research is required to confirm and identify the drivers for this observation and how it interacts with menopausal status.

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Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

Data were accessed according to Hoffmann-La Roche's policy and process for clinical study data sharing and are available by request through Vivli at https://vivli.org/.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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