Placebo Response in Rheumatoid Arthritis Clinical Trials

Katie Bechman, Mark Yates, Sam Norton, Andrew P. Cope, and James B. Galloway

ABSTRACT. ***Objective.*** Understanding the placebo response is critical to interpreting treatment efficacy, particularly for agents with a ceiling to their therapeutic effect, where an increasing placebo response makes it harder to detect potential benefit. The objective of this study is to assess the change in placebo responses over time in rheumatoid arthritis (RA) randomized placebo-controlled trials (RCT) for drug licensing authorization.

Methods. The Cochrane Controlled Trials Register database was searched to identify RCT of biological or targeted synthetic disease-modifying antirheumatic drugs (DMARD) in RA. Studies were excluded if patients were conventional synthetic DMARD (csDMARD)–naive, not receiving background csDMARD therapy, or were biologic experienced. Metaregression model was used to evaluate changes in American College of Rheumatology (ACR) 20, ACR50, and ACR70 treatment response over time.

Results. There were 32 trials in total: anti–tumor necrosis factor therapy (n = 15), tocilizumab (n = 4), abatacept (n = 2), rituximab (n = 2), and Janus kinase inhibitors (n = 9). From 1999 to 2018, there was no significant trend in the age or sex of patients in the placebo arm. Disease duration, swollen joint count, and 28-joint count Disease Activity Score using erythrocyte sedimentation rate at baseline all significantly declined over time. There was a statistically significant increase in placebo ACR50 and ACR70 responses (ACR50 $\beta = 0.41$, 95% CI 0.09–0.74, $p = 0.01$; ACR70 $\beta = 0.18$, 95% CI 0.04–0.31, $p = 0.01$) that remained significant after controlling for potential confounders.

Conclusion. There has been a rise in the placebo response in RA clinical trials over the last 2 decades. Shifting RA phenotype, changes in trial design, and expectation bias are possible explanations for this phenomenon. This observation has important implications when evaluating newer novel agents against established therapies. (J Rheumatol First Release August 15 2019; doi:10.3899/jrheum.190008)

Key Indexing Terms:
RHEUMATOID ARTHRITIS SYSTEMATIC REVIEW STUDY DESIGN PLACEBO
OUTCOME MEASURES AMERICAN COLLEGE OF RHEUMATOLOGY RESPONSE

Novel therapies in rheumatoid arthritis (RA) are coming to market with increasing regularity. It is a challenge for clinicians to comprehend how different drugs compare with each other, particularly because few head-to-head trials are conducted. This has led to a growing reliance on network metaanalyses that rely on indirect comparisons linking multiple interventions to a fixed common comparator, typically a placebo. The assumption is that results from different trials are sufficiently homogeneous in their patient characteristics, settings, and outcomes to allow pooling of the data[1].

Placebos are not inert. They cannot shrink tumors or heal fractures, but they do have an effect on symptoms modulated by the brain, particularly the perception of disease. A placebo may be very effective in reducing pain and modifying mood. Randomized controlled trials (RCT) in inflammatory arthritis use the 28-joint count Disease Activity Score (DAS28) or American College of Rheumatology (ACR) response as key outcome measures. These are composite scores that combine objective evidence of inflammation that are unaffected by placebo, and subjective measures of disease activity, which may be more amenable.

In antidepressant and antihypertensive drug trials, the magnitude of placebo response is trending upward[2,3,4,5]. It is important to appreciate this when interpreting treatment efficacy, particularly for agents with a ceiling to their thera-

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This work was primarily supported by Medical Research Council as a Clinical Training Research Fellowship to KB (CTRF- MR/R001332/1 to K. Bechman). JBG has received honoraria from Pfizer.

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Accepted for publication April 6, 2019.

peutic effect, where no matter how efficacious the drug, there is a maximum number of people who will achieve disease control. In this circumstance, an increasing placebo response will make it harder to detect quantifiable benefit. This phenomenon is apparent when looking across targeted drug trials in RA, where therapeutic improvements have largely plateaued.

The aim of our study was to assess whether placebo response is rising in RA RCT used for drug licensing authorization.

MATERIALS AND METHODS

The study was conducted in accordance with the preferred reporting items for systematic reviews and metaanalysis guidelines[6]. The systematic review was registered with the international prospective register of systematic reviews (registration number: CRD4201810521). Ethics board approval was not required for this study.

The Cochrane Controlled Trials Register databases were searched systematically for all biological or targeted synthetic disease-modifying antirheumatic drugs (bDMARD, tsDMARD) that are licensed for the treatment of RA in the UK. The search terms were "rheumatoid arthritis" and either "infliximab," "adalimumab," "etanercept," "certolizumab," "golimumab," "abatacept," "tocilizumab," "sarilumab," "rituximab," "tofacitinib," "baricitinib," or "upadacitinib." The search was undertaken in June 2017 and rerun prior to the final analysis to identify further studies that could be retrieved for analysis.

English language publications of phase II and III RCT published by July 2018 were sought. Conference abstracts were excluded. RCT were included if they met the following criteria: (1) the study provided a placebo comparator; (2) the placebo comparators were not conventional synthetic DMARD (csDMARD)–naive at enrollment and were receiving background csDMARD therapy during followup study; and (3) fewer than 15% of participants were biologic-experienced. Studies presenting duplicate data were excluded. No restrictions were applied on the length of followup. Titles and abstracts of studies retrieved using the search strategy detailed above were screened independently. The full text of the potential studies for inclusion were retrieved and assessed for eligibility.

The primary outcome of interest was treatment response, measured using the ACR criteria, defined as 20%, 50%, or 70% improvement in both tender and swollen joint count, and in 3 of the 5 core measures: patient assessment, physician assessment, pain scale, disability/functional questionnaire, and acute-phase reactant [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)]. Analyses were undertaken using Stata 14. Metaregression was used to evaluate changes in ACR20, ACR50, and ACR70 treatment response over time. A multivariate model was applied adjusting for age, sex, disease duration, baseline tender joint count, swollen joint count, CRP at baseline, and time to primary outcome.

RESULTS

Study characteristics. The literature search identified 1828 trials in total, of which 141 were either phase II of III RCT. There were 109 studies that were excluded because they enrolled patients who were csDMARD-naive, had no background csDMARD therapy during followup, had a high percentage of previous biologic exposure, or did not include a placebo comparator. All Japanese bridging studies were excluded.

There were 32 trials in total, 15 RCT evaluating anti–tumor necrosis factor therapy: adalimumab (n = 3), etanercept (n = 3), infliximab (n = 2), certolizumab pegol (n = 3), and golimumab (n = 4; Table 1). The remaining RCT evaluated tocilizumab (n = 4), abatacept (n = 2), rituximab (n = 2), and Janus kinase (JAK) inhibitors (n = 9). Studies were published from 1999 to 2018, with a median time to primary outcome of 24 weeks (range 8–52 weeks). This duration on placebo has shortened over the last 20 years (β –0.44, 95% CI –0.87 to –0.004; p = 0.048). On average, assessment visits were 4 weeks apart, with half of the studies arranging more frequent visits at study initiation. There were no trends in the frequency of study visits across the time period. All studies recruited from North America and/or Europe. From 2008 onward, a greater number of studies recruited patients from Latin America and Southeast Asia.

Patient characteristics. The median number of patients in placebo arms was 128 [interquartile range (IQR) 66–212). The mean age was 53 years (SD 2), and 79% (SD 5%) of patients were female. From 1999 to 2018, there was no significant trend in the age or sex of patients in the placebo arm (age β –0.05, 95% CI –0.23 to 0.12, p = 0.56; and sex β = 0.16, 95% CI –0.21 to 0.52, p = 0.39). Excluding the 2 studies that recruited patients with early RA (duration disease < 1 yr; Table 1, Maini 2006 and Moreland 2012), the mean duration of disease was 8.7 years (SD 2). This fell significantly across the time period studied (β –0.22, 95% CI –0.35 to 0.10, p = 0.001).

There were no significant trends in csDMARD exposure. The median methotrexate dose was 16 mg (IQR 15–17). Over two-thirds of the studies reported data on glucocorticoid exposure, which was administered in 58% (50–69%) of patients and had fallen across the time period studied (β –1.00, 95% CI –1.94 to –0.06, p = 0.04). More recent studies included a greater proportion of patients with prior biologic exposure. Prior to 2008, the average percentage exposure was less than 1% compared with 4% from 2008 onward. There were significant trends in baseline disease activity over time, with falling tender joint counts [median 28 (IQR 24–30), β –0.26, 95% CI –0.46 to –0.05, p = 0.02], swollen joint counts [median 17 (IQR 15–21), β –0.26, 95% CI –0.42 to –0.09, p = 0.003], and DAS28-ESR, despite this variable not being reported in any study prior to 2004 [mean DAS28-ESR 6.47 (SD 0.31), β –0.05, 95% CI –0.08 to –0.02, p = 0.001]. There was no trend in patient's or physician's global assessment (β –0.07, 95% CI –0.14 to 0.29, p = 0.48; and β –0.04, 95% CI –0.31 to 0.22, p = 0.75, respectively).

Changing placebo responses. ACR responses are shown in Figure 1. The median (IQR) percentage of patients in placebo arms achieving ACR response was ACR20 31% (25–39), ACR50 10% (8–16), ACR70 3% (2–5). Considering placebo arm size, there was a statistically significant increase in placebo ACR50 and ACR70 responses from 1999 to 2018 (ACR50 β 0.39, 95% CI 0.04–0.75, p = 0.03; and ACR70 β 0.17, 95% CI 0.02–0.32, p = 0.02). There was no statistically significant change in ACR20 response.

One trial had an outlier ACR70 response (Table 1, Maini

Table 1. Published randomized placebo-controlled trial of biologics and JAK inhibitors in rheumatoid arthritis between 1999 and 2018.

Year	Author	Drug	PBO, n	Recruitment Site; visits/ week	Age, Yrs, Mean (SD)	Female, %	Duration, Yrs, Mean (SD)	TJC68, Mean (SD)	SJC66, Mean (SD)	DAS28, Mean	ACR20, %	ACR50, %	ACR70, %
1999	Weinblatt[18]	ETN	30	USA, CAN; 4	53	73	13	28	17	–	27	3	0
1999	Maini[19]	IFX	88	USA, CAN, EU; 4	50 (11)	80	10 (7)	27 (24)	20 (11)	–	20	5	0
2003	Weinblatt[20]	ADA	62	USA, CAN; 2†	56 (11)	82	11 (8)	29 (15)	17 (10)	–	15	8	5
2003	Kremer[21]	ABA	119	USA, CAN EU AUS, SA; 4	54 (11)	66	9 (8)	29 (13)	22 (9)	–	35	12	2
2003	Furst[22]	ADA	318	USA, CAN; 4†	56 (12)	79	12 (10)	28 (14)	21 (11)	–	35	11	4
2004	Keystone[23]	ETN	53	USA, CAN; 8	55 (15)	72	12 (10)	25 (20)	19 (18)	–	19	6	2
2004	Keystone[24]	ADA	200	USA, CAN; 4†	56 (12)	73	11 (9)	28 (14)	19 (10)	–	30	10	3
2004	Edwards[25]	RTX	40	EU, CAN, AUS, ISR; 4†	54 (11)	80	11 (7)	32 (13)	19 (10)	6.9	38	13	5
2006	Kremer[26]	ABA	219	USA, CAN, EU, MEX; 4†	50 (12)	82	9 (7)	32 (14)	22 (9)	6.4	40	17	7
2006	Maini[27]	TCZ	49	EU; 2	51	78	0.9	16*	12*	6.8	41	29	16
2008	Smolen[28]	TCZ	204	Worldwide; 4	51 (12)	78	8 (7)	33 (16)	21 (12)	6.8	26	11	2
2008	Kay[29]	GOL	35	USA, CAN, EU, AUS; 4†	55 (11)	74	6 (2)	26 (17)	14 (6)	6.5	37	6	0
2008	Schiff[30]	IFX	165	Worldwide; 4	49 (12)	87	7 (6)	32 (15)	20 (8)	6.8	42	20	9
2008	Genovese[31]	TCZ	413	Worldwide; 4	54 (13)	84	10 (9)	29 (15)	19 (11)	6.6	25	9	3
2008	Keystone[32]	CZP	199	Worldwide; 2†	52 (11)	84	6 (4)	30 (15)	21 (10)	7.0	14	8	3
2009	Keystone[33]	GOL	133	Worldwide; 4	51 (12)	82	7 (2)	20 (8)	13 (8)	6.0	33	10	4
2009	Smolen[34]	CZP	127	EU; 2†	52 (12)	84	6 (4)	30 (13)	22 (10)	6.8	9	3	1
2010	Kremer[35]	GOL	129	Worldwide; 4	50	80	7	28	16	–	25	9	3
2010	Emery[36]	RTX	172	Worldwide; 4–8	52 (12)	86	8 (8)	30 (16)	21 (11)	6.5	23	9	5
2011	Kremer[37]	TCZ	393	Worldwide; 4†	51 (12)	83	10 (7)	28 (15)	17 (9)	6.5	27	9	1
2012	van Vollenhoven[38]	TOF	56	Worldwide	56 (14)	77	7	27	17	6.6	28	16	5
2012	Kremer[39]	TOF	69	Worldwide; 4	53 (13)	81	9	22	16	6.1	33	17	6
2012	Choy[40]	CZP	121	USA, EU; 4†	56 (12)	66	10 (8)	31 (13)	22 (10)	6.3	23	6	2
2012	Moreland[41]	ETN	255	USA; 6	49 (13)	69	0.2	14 (7)*	13 (6)*	5.8	40	22	4
2013	Weinblatt[42]	GOL	197	USA, CAN; 4†	51 (11)	80	7 (7)	26 (14)	15 (9)	5.9◊	32	13	5
2013	Kremer[43]	TOF	79	Worldwide; 4†	51 (11)	80	11 (8)	27 (17)	15 (10)	6.4	31	13	3
2013	van der Heijde[44]	TOF	81	Worldwide; 4–8	53 (12)	80	11 (9)	23 (13)	14 (8)	6.3	25	8	2
2015	Keystone[45]	BARI	98	USA, CAN, MEX, IND; 4†	49 (12)	87	5 (4)	22 (12)	16 (9)	6.3	41	9	5
2016	Genovese[46]	UPA	50	USA, EU, SA; 2	55 (12)	76	6 (5)	29 (16)	19 (12)	5.6◊	46	18	6
2017	Dougados[47]	BARI	228	Worldwide; 4†	51 (13)	83	7 (8)	24 (15)	13 (7)	6.2	39	13	3
2017	Taylor[48]	BARI	488	Worldwide; 4†	53	78	10 (9)	23 (14)	16 (9)	6.4	40	17	5
2018	Burmester[49]	UPA	221	Worldwide; 4†	56 (12)	75	7 (8)	25 (15)	15 (9)	5.6◊	36	15	6

† Visits initially at weeks 1 and 2, followed by either 2 or 4 visits weekly as indicated. * 28-joint count. ◊ DAS-CRP. Other DAS28 results reflect DAS28 with ESR. JAK: Janus kinase; PBO: placebo; TJC: tender joint count; SJC: swollen joint count; DAS28: 28-joint count Disease Activity Score; ACR: American College of Rheumatology; ETN: etanercept; IFX: infliximab; ADA: adalimumab; GOL: golimumab; CZP: certolizumab pegol; RTX: rituximab; ABA: abatacept; TOF: tofacitinib; BARI: baricitinib; UPA: upadacitinib; CAN: Canada; EU: Europe; AUS: Australia; SA: South Africa; ISR: Israel; MEX: Mexico; IND: India; TCZ: tocilizumab; ESR: erythrocyte sedimentation rate.

2006, tocilizumab). Excluding this study did not alter the findings with comparable changes in ACR response (ACR50 β 0.41, 95% CI 0.09–0.74, p = 0.01) and (ACR70 β 0.18, 95% CI 0.04–0.31, p = 0.01), although the trend in ACR20 responses become statistically significant (β 0.70, 95% CI 0.03–1.38, p = 0.04). For each additional year there is around a 0.5 percentage point increase in ACR50 treatment response, which over 10 years equates to a 5% increase in ACR50 response. The changes in ACR50 and ACR70 responses remained significant after adjustment for age, sex, disease duration, baseline tender joint count, swollen joint count, CRP, and time to primary outcome.

We considered other factors that may influence or explain the placebo response. This included looking in parallel at treatment response in the therapeutic arm over time, which did not change. We looked at RA disease duration, which did have an effect on placebo ACR50 response (β –0.84, 95% CI –1.4 to –0.19, p = 0.01) but not ACR20 or ACR70. Finally, we examined the inclusion of CRP or ESR at recruitment; however, there were inadequate data to draw firm conclusions.

DISCUSSION

This analysis confirms significant increases in both ACR50 and ACR70 treatment responses in patients in the placebo arm of RA RCT from 1999 to 2018. This remained statistically significant after controlling for potential confounders. These results have important clinical implications and should be acknowledged when comparing efficacy between emerging and established therapies.

There are several possible explanations for the rise in placebo response. RA severity has decreased over time, a

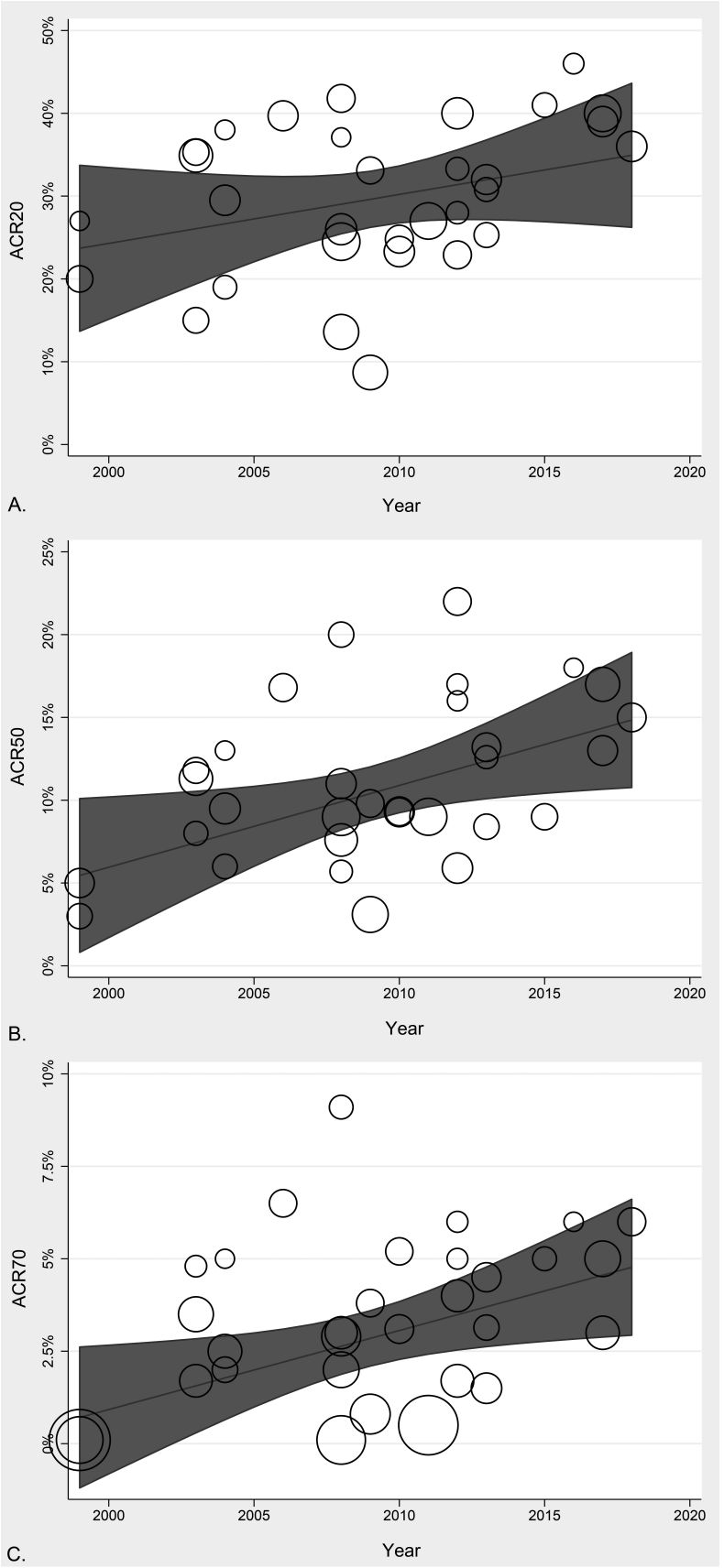

Figure 1. Adjusted ACR responses in the placebo arm of published randomized controlled trials of biologics and JAK inhibitors in rheumatoid arthritis between 1999 and 2018. A. ACR20. B. ACR50. C: ACR70. ACR: American College of Rheumatology; JAK: Janus kinase.

reflection of the emphasis on early diagnosis and improvements in pharmacological therapies[7,8]. This has reduced the pool of potential patients who meet eligibility criteria, which may result in investigators inflating baseline disease scores to enable entry into a study. This is particularly relevant for industry-funded trials in which clinical units are financially compensated for study participation. The course of RA has also changed over time. Patients sustain lower disease activity levels, interspersed with episodes of increased activity defined as "flares." It is plausible that a proportion of patients are recruited during a flare that spontaneously resolves, and consequently their followup disease score reflects a significant improvement from baseline.

Changes in trial design may account for the rise in placebo response. There has been a shift in the geographical distribution of RA trial sites, with greater recruitment from Latin America and Eastern Europe. In resource-poor countries, trial participation would improve adherence to background csDMARD, amplifying placebo response. An analysis of 981 placebo subjects across worldwide RA trials reported a consistently higher placebo response in patients recruited from Latin America. The same study also identified higher odds of ACR20 response in Asian patients compared to whites[9]. A shift in the recruitment of patients with different cultural beliefs may have contributed to an increased response to the Hawthorne effect. This is defined as an additional clinical response resulting from increased attention provided by participation in the clinical trial, a phenomenon described in RA studies[10].

The rise in placebo response may also be related to recent changes in the use of background csDMARD, with recommendations for combination therapy early in the disease. Because maximal response to csDMARD is seen at 6 months, RCT requiring only 3 months of background therapy may be associated with higher placebo effect[11]. The formulation of a placebo may also influence response. Research has suggested that patient perceptions of placebo are influenced by its color, size, and form; injections elicit a stronger placebo effect than oral medications, while capsules are perceived to be "stronger" than tablets[12]. Interestingly, the more recent studies in this analysis assessed oral JAK inhibitors and thus used an oral placebo comparator. This is in contrast to the earlier biologic RCT that evaluated injectable placebo, which one would expect to elicit a stronger placebo effect. Last, the desire for the new treatments to succeed can result in implicit bias in both subject and investigator-controlled outcomes.

Expectation bias, the awareness that a new drug being administered imparts an expectation benefit to both the investigators and the recipients, may also contribute to the rising placebo response. Outcome expectation is based on patients' understanding of the treatment offered, their own illness, and experiences with past treatments. In antidepressant clinical trials, patient expectancy is a chief mechanism for placebo response. Perceived prestige, credibility, and sophistication of a treatment can significantly increase expectations of improvement[13]. It would be unusual for this to affect objective biological responses, but it is plausible that expectation bias influences subjective measures of disease activity. With the decline over time in the severity of objective markers of inflammation, the effect of expectation bias on subjective measures of disease activity may be substantial.

The identification of biomarkers of a placebo response would be a powerful tool in improving the interpretability of trials and assisting in stratifying populations and adjusting effect sizes. Measuring expectation benefit to identify participants susceptible to a placebo effect would be valuable, although no fully validated method exists[14].

We did not demonstrate a significant increase in ACR20 treatment responses in patients in the placebo arm of RA RCT from 1999 to 2018. A possible explanation for this is that despite its high specificity, unlike ACR50 and ACR70, the ACR20 has demonstrated only modest sensitivity for patient-reported improvement[15]. This suggests that patients who judged themselves to have improved do not demonstrate an associated ACR20 response, and may explain the absence of an increase over time.

Our goal was to understand changing placebo responses over time. There is a growing number of RCT recruiting patients with previous biologics exposure. However, there is a noticeable difference in treatment effect between patients who are biologic-naive versus those who have had no response with one, or perhaps even multiple, biologics. In this study, the restricted search criteria increased homogeneity among the placebo patients and facilitated a cohort that was representative of current practice. However, we could not control for all differences in the study populations and trends in study quality. Unfortunately, there is very little published data on the socioeconomic or educational level of the patient populations included in each RCT. It is acknowledged that these factors influence placebo responses, although substantial research has not yet identified a consistent demographic characteristic that predicts placebo response[16]. The results are potentially influenced by publication bias, with undersampling of placebo responses from failed trials. If a trial had a large placebo response, it is likely that it failed to demonstrate a positive therapeutic advantage and therefore was less likely to be published. We did not consider the effect of the nocebo effect, a phenomenon in which patients' concerns and expectations about the value of a therapeutic intervention reduce adherence and treatment response. This has been considered in patients switching biologics from bio-originators to biosimilars, to explain a deterioration in therapeutic benefit[17]. How the nocebo effect influences RA trials over time has not been examined and is an area for potential further study.

This study has demonstrated an increase in treatment response in the placebo arm of RA trials. It is essential that we improve our understanding of the mechanisms behind this

phenomenon. A rising placebo response has important implications when comparing the efficacy of treatments across clinical trials, including in network metaanalyses. Estimates of drug efficacy within a trial are unlikely to be confounded by the placebo response, because this is expected to be equal in both the placebo and active comparator arm. However, in trials in which there is a therapeutic ceiling effect, as seen in RA, an increasing placebo response rate will result in a reduced treatment effect size. This will affect comparisons between established and novel agents and should be considered by clinicians when evaluating the efficacy of different therapies.

ACKNOWLEDGMENT

We acknowledge Dr. Rahul K. Patel, MD, Senior Medical Director, PRA Health Sciences, Raleigh, North Carolina, USA, for his detailed consideration of our research and the valuable contribution he made to the final manuscript.

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