Placebo Response in Rheumatoid Arthritis Clinical Trials

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Hello, I'm Dr. James B. Galloway. I'm delighted that our paper on the placebo response in rheumatoid arthritis (RA) trials has been selected this month by the editor Dr. Earl D. Silverman, and I'm going to say a few words on behalf of Dr. Katie Bechman, who is actually the first author of this study, but unfortunately isn't available to do this recording.

I will structure this on a few words about what we found. I will briefly say why we did this study and our reasoning for undertaking this project was in the first place. And also briefly mention our methodology, so you can try to understand the risk of bias in the findings and how much you can trust our results.

So the headline of what we have described is that if you consider the American College of Rheumatology (ACR) 20 response for clinical trials of patients with RA, which is a common outcome measure that has been used in the many of the majority of the clinical trials over the last 20 years, then the proportion of patients who achieve an ACR20 in the placebo arm has been steadily rising.

If you look at trials from 20 years ago, for example, you see that typically 20% of people, often fewer, would achieve an ACR20 in the placebo arm. In the last five years, we've not seen any clinical trials where the ACR20 response has been below 30%. In fact, many of them have been above 40% and some as close as 50% in the placebo arm achieving that treatment response.

This always has important implications when we are interpreting clinical trials of new drugs in the field. So the reason we wanted to take this study was partially our own personal observation across the congresses in Europe and the United States (US) over the last 10 years. We've seen these rising reported rates of placebo response. In fact, with some of the JAK inhibitors — a class we've seen data coming out, particularly in the last couple of years from clinical trials — we've seen placebo arm responses from sub-populations from certain geographic distributions hitting the 50% mark. We wanted to investigate this.

Another bit of background, there's an awareness in clinical trials in other disease areas, for example, hypertension, that placebo responses have also been climbing.

So why might this be? Well, there are a few things that crossed our minds. The first thing is in RA, we have a situation where people with RA have fluctuating disease activity. They have episodic flare sometimes. As many of our clinical trials require people to have severe disease at the point of study entry, it may be possible that we are increasingly capturing people during states of transient flare when they enter the trial. Those people who are transiently flaring will get better whatever we do, the effect we might return to the regression of the mean. And it could be that some of the increasing placebo responses is because we are recruiting a large number, a large portion of patients, who are in a flare rather than patients who have sustained severely active rheumatoid.

Second is the possibility that we are seeing the effect of geography. In high healthcare resource countries, there are many treatments available to manage RA. A challenge of this is that it's hard to recruit patients into studies when many treatments are already on the table for them. As a result, unsurprisingly, we have seen a growing number of clinical trials taking place in countries that have less healthcare resources available. The clinical trials then provide a means of access to treatment. I admit

this is not something I am saying is the next phenomena. I am an advocate for clinical trials, and I am an advocate for getting wider access to treatment for patients. But consider this: in a resource-poor setting, when you take part of a clinical trial, you not only get enrolled in a study and given regular followup, perhaps more frequent followup than you would otherwise receive, but you also have other medication supplied and paid for during the study, for example, methotrexate (MTX), your background immune-suppression therapies. And if those hadn't been regularly administered prior to the study entry, actually what we may be doing when we enroll people into clinical trials is looking at interventions which not only include the new drug but also introduction of standard of care, which may not have been fully available prior to the entry of the trial.

Thirdly, of course, we have to acknowledge that there may be changes in expectation in health care. We have seen an enormous evolution of healthcare across all fields of medicine. And there may be an expectation by us of patients as to what they expect from treatments and how well a drug may work. These we talk about in the discussion and if anyone wants to write a comment, I suspect we haven't got a single reason for the rising placebo response, but rather it's a complex and combined effect of many facets of clinical trial design and conduct. Irrespective of the cause of it, it is definitely happening, I believe.

We, in terms of our methods, I will just say very briefly what we did to reach these conclusions. It was a systematic review which we conducted looking for clinical trials of new drug interventions in RA. Our primary source when we did the search was the Cochrane Controlled Trials Register database. We expanded that looking for other trials through links or through congresses we were aware of. In our approach, we used a metaregression, and we did that so that we could account for differences in patient characteristics in the different trials, such as the differences in age or disease severity at trial enrollment. So we could account for those when we looked at the impact of the ACR20 response. We also present ACR50 and ACR710 responses. For those people who are reading the paper, I think Figure 1 is a really important figure, in which we present graphically the placebo response across the papers and across the trials we report on.

I hope you enjoy the paper and I'm very grateful for *The Journal of Rheumatology* for selecting it as an Editor's Pick.

Thank you.