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To cite this article: Yoshiya Tanaka & Samuel H. Zwillich (2016) Response to Dr Minota's Letter to the Editor of Modern Rheumatology Regarding a Study of Tofacitinib in Japanese Patients with Rheumatoid Arthritis, Modern Rheumatology, 26:2, 318-319, DOI: 10.3109/14397595.2015.1012799

To link to this article: https://doi.org/10.3109/14397595.2015.1012799

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Published online: 24 Feb 2016.
LETTER

Response to Dr Minota’s Letter to the Editor of Modern Rheumatology Regarding a Study of Tofacitinib in Japanese Patients with Rheumatoid Arthritis

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In Response:

We thank Dr. Seiji Minota for his thought-provoking comments on the article [1] as well as questions on the inclusion of the American College of Rheumatology 20% improvement criteria (ACR20) response rates in tofacitinib promotional materials.

The tofacitinib clinical trial (NCT00603512) by Tanaka et al. [2] was conducted in phase 2 to explore the possibility of enrolling Japanese patients with rheumatoid arthritis (RA) in the phase 3 multinational clinical trial (NCT00847613), which was reported by van der Heijde et al. [3] A target sample size of 125 patients (5 treatment groups of 25 patients per group) was required to provide at least 80% power and a 5% significance level, one-sided testing, to detect a trend of dose–response using the Cochran–Armitage trend test on ACR20 response rates. The Cochran–Armitage test was highly positive (p < 0.0001) and the ACR20 response rates, as calculated by last observation carried forward (LOCF), are as quoted in Dr. Minota’s letter [1]. However, while the odds ratio for ACR20 responses on tofacitinib 5 mg twice daily compared with those on placebo described in Dr. Minota’s letter [1] was calculated correctly, we have several concerns with his contextualization of the odds ratio:

1. Any interpretation of this odds ratio is severely limited by the small size of the trial and the resulting wide range of its 95% confidence limits (16.3, 1495.6).
2. The clinical trial by Kremer et al. [4], to which these results are compared, reported primary efficacy results at week 12 based on non-responder imputation (NRI), not LOCF. The ACR20 response rates on tofacitinib 5 mg twice daily in the Kremer study when calculated at week 12 by LOCF are higher, 62.0%, than those calculated by NRI, 50.7%, and the corresponding odds ratio for ACR20 responses calculated by LOCF is slightly larger, 2.7 (95% confidence limits: 1.36 and 5.34).
3. The clinical trial by Kremer et al. [4], while similar in design to the study by Tanaka et al. [2] in phase (phase 2), tofacitinib doses studied, and the requirement for inadequate response to stable background methotrexate, showed the lowest treatment effect size for tofacitinib of all the studies of tofacitinib in RA conducted to date. Therefore, comparison to the results of this study is not representative of comparison to the larger body of evidence demonstrating the effect size of tofacitinib. We cannot explain the variation in effect size by study on a quantitative basis, and believe that our descriptive and non-quantitative observation that the response rates were higher in the Tanaka study remains the most appropriate.

While adherent with the Pharmaceutical Affairs Law and relevant self-regulations, and originally intended to present the development program results in chronological order, Pfizer understands how the appearance of the figure in the Specifying Product Information Summaries or commercial bulletins describing the study by Tanaka et al. first has a potential risk to elicit misunderstanding among health care professionals, who may assume this is a phase 3 study that represents the efficacy observed in the global development program. Thus, Pfizer has decided to change the order of clinical results by presenting confirmatory phase 3 results first followed by other clinical results including those from this phase 2 study. Pfizer Japan is committed to the appropriate promotion of tofacitinib and the accurate presentation of the efficacy and safety profile of tofacitinib by our company representatives.

Finally, we agree with Dr. Minota that the results of the postmarketing surveillance (PMS) are important. Pfizer is strongly committed to conduct the PMS with all case registration to investigate and publish the long-term safety and efficacy profile of tofacitinib in Japanese RA patients in a real-world setting.

Conflict of interest

Y. Tanaka has received consulting fees, speaking fees, and/or honoraria from Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi-Tanabe, Pfizer, Janssen, Eisai, Daiichi-Sankyo, UCB, GlaxoSmithKline, and Bristol-Myers; and has received research grants from Mitsubishi-Tanabe, Chugai, MSD, Astellas, and Novartis. SH Zwillich is a Pfizer employee. This study was sponsored by Pfizer.
References


