Letter to Editor Rheumatology
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An international open-access and peer-reviewed online journal

Letter

Lett Ed Rheumatol
doi:10.2399/ler.11.0001

Differences in levels of disease activity in rheumatoid arthritis patients from different countries

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Abstract

In a report of a multinational trial of a new Sky inhibitor (R788) among patients with rheumatoid arthritis with unsatisfactory response to methotrexate, the authors did not include the baseline methotrexate dose among patients from different geographies. This information is important for a fair assessment of this trial.

Dear Editor,

In September 30th issue of the New England Journal of Medicine (NEJM), Weinblatt et al. report that a new Syk inhibitor (R788) is more efficacious in patients with rheumatoid arthritis (RA) from Eastern Europe and Latin America versus from the USA, in a randomized, double blind trial of patients who RA despite long-term treatment with methotrexate (MTX).[1] They also indicate in the Discussion section that they cannot explain this result. However, patients with RA from economically disadvantaged countries have substantially poorer clinical status than those from rich countries,[2] and therefore have considerably greater capacity for improvement. Furthermore, low socioeconomic status is a more significant risk factor for poor status in RA than age or duration of disease,[3] and predicts mortality in RA at higher levels of significance than laboratory tests or radiographs, asrecognized by one of the authors.[4] Low education level predicts excess mortality rates in cardiovascular disease, as reported in the NEJM in 1984,[5] as well as in most chronic diseases.

Another concern involves the average dose of MTX used by patients prior to enrollment. All patients were classified incomplete responders to methotrexate, although the range of MTX doses at entry is reported at the wide range of 7.5 mg-25 mg a week. Most recent clinical trials involving new biologic agents, particularly from the US, have involved MTX use at higher doses of 20-25 mg a week in most patients. It is quite possible that patients from outside the USA were considered methotrexate failures at lower doses than the USA patients, to be eligible for the trial. Inclusion of these patients, if in high enough a number, would skew the responses seen in this trial to the benefit of the agent tested. Baseline methotrexate doses, as well as clinical status and responses, in the 6 different countries would surely enhance interpretation of the outcomes in this trial.

References

1. Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. *N Engl J Med* 2010; 363:1303-12.

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Citation: Yazici Y, Yazici H, Pincus T. Differences in levels of disease activity in rheumatoid arthritis patients from different countries. Lett Ed Rheumatol 1(1):e110001. doi:10.2399/ler.11.0001

Received: November 23, 2010; **Accepted:** December 11, 2010; **Published:** February 15, 2011

Conflicts of Interests: The authors have declared that no conflicts of interests exist.

2. Sokka T, Kautiainen H, Pincus T, et al. Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. *Ann Rheum Dis* 2009; 68:1666-72.
3. Callahan LF, Smith WJ, Pincus T. Self-report questionnaires in five rheumatic diseases: comparisons of health status constructs and associations with formal education level. *Arthritis Care Res* 1989;2:122-31.
4. Lee SJ, Kavanaugh A. A need for greater reporting of socioeconomic status and race in clinical trials. *Ann Rheum Dis* 2004; 63:1700-1.
5. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. *N Engl J Med* 1984;311:552-9.

Background and Editor's Note:

The above letter was initially submitted to the New England Journal of Medicine and was rejected. The abstract of this paper by Weinblatt et al. is presented here.

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Associate Editor, LER

An oral spleen tyrosine kinase (SYK) inhibitor for rheumatoid arthritis

Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB.
N Engl J Med. 2010 Sep 30;363(14):1303-12.

Background: Spleen tyrosine kinase (Syk) is an important modulator of immune signaling. The objective of this phase 2 study was to evaluate the efficacy and safety of R788, an oral inhibitor of Syk, in patients with active rheumatoid arthritis despite methotrexate therapy.

Methods: We enrolled 457 patients who had active rheumatoid arthritis despite long-term methotrexate therapy in a 6-month, double-blind, placebo-controlled trial. The primary outcome was the American College of Rheumatology (ACR) 20 response (which indicates at least a 20% reduction in the number of both tender and swollen joints and improvement in at least three of five other criteria) at month 6.

Results: R788, at a dose of 100 mg twice daily and at a dose of 150 mg once daily, was significantly superior to placebo at month 6 (ACR 20 response rates of 67% and 57%, respectively, vs. 35%; P<0.001 for the comparison of both doses with placebo). It was also significantly superior with respect to ACR 50, which indicates at least a 50% improvement (43% and 32% vs. 19%; P<0.001 for the comparison of the 100-mg dose with placebo, P=0.007 for the comparison of the 150-mg dose with placebo) and ACR 70 (28% and 14% vs. 10%; P<0.001 for the comparison of the 100-mg dose with placebo, P=0.34 for the comparison of the 150-mg dose with placebo). A clinically significant effect was noted by the end of the first week of treatment. Adverse effects included diarrhea (in 19% of subjects taking the 100-mg dose of R788 vs. 3% of those taking placebo), upper respiratory infections (14% vs. 7%), and neutropenia (6% vs. 1%). R788 was associated with an increase in systolic blood pressure of approximately 3 mm Hg between baseline and month 1, as compared with a decrease of 2 mm Hg with placebo; 23% of the patients taking R788 vs. 7% of the patients receiving placebo required the initiation of or a change in antihypertensive therapy.

Conclusions: In this phase 2 study, a Syk inhibitor reduced disease activity in patients with rheumatoid arthritis; adverse events included diarrhea, hypertension, and neutropenia. Additional studies will be needed to further assess the safety and efficacy of Syk-inhibition therapy in patients with rheumatoid arthritis.

(Funded by Rigel; ClinicalTrials.gov number, NCT00665925.)

