Biologic agents in rheumatoid arthritis: temporal trend of incremental benefits

Andrea Messori, Dario Maratea, Valeria Fadda and Sabrina Trippoli

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In evaluating the efficacy of biologic agents in rheumatoid arthritis (RA), one interesting feature of the meta-analysis by Favalli and colleagues [Favalli *et al.* 2012] is that outcomes were expressed as damage progression (namely, annual radiographic progression [ARP] rate). Although expressing outcomes this way raises a number of methodologic issues, the methods adopted by Favalli and colleagues were accurate and convincing, and so their analysis offered a new perspective for interpreting the benefits of biologic agents.

The initial analysis of Favalli and colleagues included 12 studies and found a mean difference of nearly –30% in the ARP rate for biologics in comparison with methotrexate as well as a high heterogeneity ($I^2 = 99\%$). After excluding the two most asymmetrical studies in the funnel plot, the plot's results were improved and the mean improvement was less pronounced (mean difference = –18.7%; 95% confidence interval: –29.9% to 7.44%); however, heterogeneity remained very high ($I^2 = 100\%$). To reduce heterogeneity, Favalli and colleagues separated the 12 trials into a subgroup including studies on early disease (5 trials) and a subgroup including studies on late disease (7 trials). Even after this separation, heterogeneity remained high ($I^2 = 97\%$ and 99% for the two subgroups, respectively).

We have re-analysed the same data included in Favalli and colleagues' study by application of metaregression. This statistical technique was applied as described previously [Messori *et al.* 2012a, 2012b; Vasques *et al.* 2012]. In performing our analysis, the metaregression first assessed two covariates ('year of publication' and 'disease stage' classified as early *versus* late) and its stepwise process left out the covariate 'disease stage' (since its

significance, $p = 0.464$, was far from the prespecified threshold of $p = 0.10$). At the next step, the results of metaregression indicated that 'year of publication' was a significant covariate.

Figure 1 illustrates these results. According to the regression line, the values of mean difference varied from –65% in 2000 to –10% in 2012. A smaller and smaller absolute difference with time (from approximately 65% in 2000 to 10% in 2012) means that the incremental effectiveness (or improvement) of biologics has decreased over the time interval examined. More importantly, this annual loss of improvement was clinically relevant and showed a clear statistical significance (annual loss of improvement 4.59%; $p = 0.014$). Interestingly enough, the residual heterogeneity found in our analysis after incorporation of this covariate was at $I^2 = 84.8\%$; as compared with the I^2 values found by Favalli and colleagues, there was a reduction in heterogeneity, although our value remained high.

In conclusion, the analysis of Favalli and colleagues has the merit of focusing on an important clinical outcome. Our metaregression of the same data suggests another interpretation, i.e. that biologics have apparently reduced, with time, their incremental benefit over methotrexate. While our findings are difficult to interpret and could simply be coincidental, investigating the main determinants of the efficacy of biologics in RA remains a matter of further study. In this framework, the various hypotheses presented by Favalli and colleagues are another step forward in the knowledge of treatments for this disease.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

Correspondence to:

Andrea Messori, PharmD
HTA Unit, Area Vasta
Centro Toscana, Regional
Health System, Via
Guimaraes 9–11,
59100 Prato, Italy
andrea.messori@estav-
centro.toscana.it

Dario Maratea, PharmD
Valeria Fadda, PharmD
Sabrina Trippoli, PharmD
HTA Unit, ESTAV Toscana
Centro, Regional Health
Service, 50100 Firenze,
Italy

Figure 1. Meta-regression analysis of temporal trends of mean difference in effectiveness between biologics and methotrexate in rheumatoid arthritis from 2000 to 2012 (12 randomized trials; data obtained from Tables 3 and 4 of Favalli *et al.* [2012]). The values of mean differences can be interpreted as mean improvements, if one disregards their algebraic sign. The regression equation was mean difference (%) = $-64.692 + 4.590 \times (\text{YEAR} - 2000)$; $p = 0.014$. Study-specific weights were calculated as inverse variance (where variance was the reciprocal of the number of patients); meta-regression analysis was based on SPSS software (Version 8.1, SPSS Inc., Illinois). Symbols: each study is represented by a circle, the diameter of which is proportional to its statistical weight; grey bubbles indicate studies of early disease ($N = 5$) while white bubbles indicate studies of late disease ($N = 7$).

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