Identifying predictors of drug effectiveness in observational studies in rheumatoid arthritis: a challenging task

Evaluation of: Agarwal SK, Glass RJ, Shadick NA *et al.*: Predictors of discontinuation of tumor necrosis factor inhibitors in patients with rheumatoid arthritis. *J. Rheumatol.* 35(9), 1737–1744 (2008). Difficulties in identifying reliable predictors of drug effectiveness in the observational setting are summarized, and the results of the Agarwal *et al.* report are put into a larger context in this evaluation. Drug survival is one of the most robust measures of drug effectiveness, but predictors thereof remain weak. Close patient monitoring and withdrawal of unsuccessful treatments remain the hallmark.

Pierre Geborek
Lund University Hospital, Department of Rheumatology, Lund SE 221 85, Sweden
Tel.: +46 46 172 287
Fax: +46 46 128 468
Pierre.geborek@med.lu.se

In the study being evaluated, the authors have attempted to identify factors that may predict future anti-TNF drug withdrawal in an observational setting [1]. Possible predictors were separated into four domains: subject characteristics, rheumatoid arthritis (RA) treatment, baseline disease activity and severity, and end of study disease activity. Using Cox proportional hazard and multiple regression modeling including backward selection steps, they find that higher disease activity during treatment, fewer cumulative methotrexate years and increasing numbers of previous anti-TNF drugs all contribute to a shorter time on current anti-TNF therapy. In contrast, prior use of traditional DMARD therapy was associated with a longer time on current anti-TNF therapy, while, surprisingly, concomitant methotrexate was not. A primary high association between Hispanic patient origin and rapid anti-TNF withdrawal disappeared in the final combined model.

Obviously, such information is important to treating physicians, but it is also important for health economic estimations and has a bearing on decisions in the healthcare system and the pharmaceutical industry. However, finding reliable predictors in the observational setting is a formidable undertaking where several factors must be considered before any generalization is alleged. These factors can roughly be classified into:

- The setting of the study (country, healthcare and insurance system, hospital/primary care, referral system versus population-based system, academic and/or office-based, use of claims databases, industry-sponsored databases, disease or therapy oriented);
- The protocol (prospective/retrospective, possible inclusion of some patients also in ongoing/previous randomized control trials, prevalent or only incident cases, classification of patients, end point/outcome of study);
- The variables included (RA Disease Activity Score [DAS], swollen/tender joint count, Health Assessment Questionnaire [HAQ] and/or multidimensional HAQ [MD-HAQ], radiograms etc.);
- And, lastly, a control system for possible selection bias, missing data and adverse events must be included.

Finally, several studies from different settings with similar patients, protocols and using congruent evaluation tools must come to comparable conclusions before predictors can be widely accepted. Unfortunately, most observational studies cannot include adequate control populations, since this would immediately rule out a large proportion of the patients in the clinical setting [2].

The authors have used information drawn from an observational study in one academic center in Boston, MA, USA, the Brigham RA Sequential Study (BRASS). The aim of the study is to help identify biomarkers and genetic indicators to predict disease activity and severity, as well as treatment response and toxicity. Thus the aim is to study both disease and therapeutical outcome, and the protocol does not include specific treatment strategies. The information is prospectively gathered biannually and seems to include mostly prevalent RA patients with established well-characterized disease. However, nothing is stated regarding the referral system,

future medicine part of fsg

number of physicians entering data, possible patients in ongoing or previous randomized control trials, or a possible effect of the medical insurance system on the actual patient population. A short note in the results section that the availability and type of medical insurance was not associated with anti-TNF discontinuation is difficult to interpret, since this variable was not entered into the regression models. Presumably the majority of the patients had insurance covering most of the medical costs. In addition, the number of Hispanic patients was presumably low because the elevated first hazard ratio for discontinuation (suggesting possible genetic as well as sociodemographic factors) had large confidence intervals and disappeared in the final combined model.

Another particularity of the current setting seems to be good function measured by a low average MD-HAQ value of 0.7, in spite of an average of 14.7 years disease duration. However, MD-HAQ is not directly comparable to the traditional HAQ since it also incorporates several more disease activity related items. However, increasing the MD-HAQ by an average of 0.3–0.5 units [3] would give HAQ levels of 1–1.2, which points to relatively good functional capacity compared with most other observational settings reporting anti-TNF drug outcome. In particular, the cited British Society for Rheumatology Biologics Register (BSRBR) has reported extremely high average HAQ levels of above 2 in their anti-TNF-treated RA patients [4]. This is presumably due to the restrictions imposed by NICE. Also, few centers reporting the outcome of anti-TNF therapy have baseline DAS levels below 5 compared with 4.2 in the BRASS cohort. Some of these differences could be due to the lack of baseline data at anti-TNF initiation in a large proportion (66%) of the BRASS cohort. Actually, baseline characteristics were only present in 170 incident cases, thus markedly reducing the power to find predictors. A statement that a sensitivity analysis did not reveal any significant differences between incident and prevalent cases does not overcome this shortcoming. Other issues pertinent to the current setting include the large proportion of patients taking anti-TNF without concomitant methotrexate (53%), and actually as many as 24% had not tested any traditional DMARDs before the current anti-TNF session. In spite of the above-mentioned items pointing to a population with relatively mild RA in the BRASS cohort, most items collected, including the presence of nodules in 43%, indicate a more severe disease in the anti-TNF-treated patients compared with RA patients not treated with anti-TNF. Another problem with the BRASS cohort remains the mixture of first/second/third anti-TNF treatment courses used in the analyses, since these are not unrelated to one another [5–7].

When searching for predictors of the success/failure of treatment regimes, the outcome measure used is crucial. The authors have chosen drug withdrawal, which in the observational setting in many ways represents the most robust issue [8–11]. The problem is of course that it can represent a very long-term outcome (more than 10 years), and that it offers little help in the short-term perspective where treatment discontinuation may be pertinent for other reasons depending on the protocol and setting (e.g., discontinuation due to lack of predefined response). The authors wisely refrained from including withdrawal reason in the model due to lack of data. However, with such information readily available, such as the BSRBR in the UK, the South Swedish Arthritis Treatment Group (SSATG) and Anti-Rheumatic Therapies In Sweden (ARTIS), the Danish Database for Biological Therapies in Rheumatology (DANBIO), the Dutch Rheumatoid Arthritis Monitoring register (DREAM) in Holland, Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología (BIOBADASER) in Spain, and the German Biologics Register (RABBIT) in Germany, this information is not all too convincing, since patients with a moderate/poor response are more inclined to stop treatment due to a perhaps mild/moderate adverse event, which would not stop drug continuation in patients experiencing a remarkable improvement. Thus, overall drug withdrawal is probably the most forceful and reliable measure. We and others have used overall anti-TNF drug withdrawal as an outcome measure [8–11]. We found that treatment with etanercept, concomitant methotrexate and low baseline disability (low HAQ) predicted better drug survival in 1161 first time anti-TNF-treated Swedish RA patients in a population-based setting [8]. Also, a higher number of previous traditional DMARDs, older age and low baseline C-reactive protein levels predicted premature anti-TNF treatment termination. Several of the European database centers report relatively consistent data (DANBIO, DREAM, BIOBADASER and SSATG). These findings are somewhat in contrast to the current BRASS data; however, differences in study setting and patient selection, as outlined above, probably offer sufficient explanations.

To evaluate effectiveness in the observational milieu, different response criteria developed for randomized controlled clinical trials have often been used as outcome measures instead of drug withdrawal. This entangles several new problems when comparing different studies. The ACR response criteria are altogether relative measures, where improvements in several disease activity measures are necessary. The European League Against Rheumatism (EULAR) response criteria using improvement in the composite DAS score comprises two components – improvement in DAS score and reaching below an absolute level. When we studied predictors of response for anti-TNF therapy we found an interesting apparent discrepancy where high baseline measures of disease activity predicted response using ACR criteria, while the opposite was true when using the EULAR criteria. The simple explanation was that lower baseline levels of DAS28 permitted patients at the group level to more easily reach below the mandatory 3.2 level for good response, while high levels of disease activity measures permit higher relative response as measured using the ACR criteria [5]. Similarly, remission (DAS28 < 2.6) is more easily reached on the group level if baseline DAS28 is lower [5,9].

The influence of previous anti-TNF treatment on treatment response has been studied in several settings, but always with relatively low numbers and limited power and/or study designs (for reference, see [5]). Overall, there seems to be a decreasing level of response with increasing numbers of anti-TNF treatments [5,7,12]. We found lower age and HAQ scores, elevated DAS28 values and having ceased the former anti-TNF treatment due to adverse events rather than inefficacy to be predictors of response. However, no variable was consistently predictive for all examined response criteria [5].

The current BRASS study used other dimensions than baseline and patient characteristics to identify predictors for drug withdrawal. The use of disease activity level during therapy might, from a purely scientific point of view, be arguable, since it does include issues other than pure baseline variables as predictors. However, since they have chosen drug withdrawal as the outcome measure, I believe this is endorsed. The reported higher disease activity measures while on treatment in patients later withdrawing therapy would be expected, since they would indicate primary or secondary treatment failure. Unfortunately, stop reasons were not consistently available, thus precluding the possibility to relate treatment characteristics to adverse events and secondary failure. We and others have reported a relationship between the formation of antibodies to the treatment remedy and subsequent secondary failure and infusion-related adverse events [13,14].

Another possibility that we have recently explored is the early response to treatment as a predictor of long-term drug survival. We found that response after 6 weeks of treatment was a good predictor of long-term drug retention. This was further enforced when response after 3 months was studied [15].

As pointed out in the current report, several other factors predicting the success of anti-TNF therapy have been studied, including genotype and presence of rheumatoid factor/anticyclic-citrullinated peptide [1,16,17]. Although theoretically interesting, they have not demonstrated their place as a firm base for treatment decisions in clinical practice at present. In addition, identifying antibodies against treatment remedies is an interesting possibility, and could perhaps be more widely used in specific patients to predict secondary failure/adverse events [13,14]. However, they cannot be applied uncritically, disregarding patient reactions to treatment.

Thus, several genetic, demographic, disease and treatment characteristics have been implicated in predicting the success of anti-TNF treatment. However, the predictive values are generally low, and cannot be uncritically used at the individual patient level. Therefore, close patient monitoring and withdrawal of unsuccessful treatments still remain the hallmark in the observational setting.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Regarding therapeutical outcome in observational studies, several factors must be considered before any generalizability is alleged:
  - The setting of the study
  - The protocol
  - The variables
  - Inclusion of a control system for possible selection bias, missing data and adverse events.
- Most observational studies cannot include adequate control populations.
- Drug withdrawal is a robust outcome measure of therapy.
- Identifying reliable predictors of drug effectiveness is difficult.
- Predictors must be corroborated from several different settings.
- Close patient monitoring and withdrawal of unsuccessful treatments remain the hallmark in the observational setting.

Bibliography

1 Agarwal SK, Glass RJ, Shadick NA *et al.*: Predictors of discontinuation of tumor necrosis factor inhibitors in patients with rheumatoid arthritis. *J. Rheumatol.* 35(9), 1737–1744 (2008).

2 Zink A, Strangfeld A, Schneider M *et al.*: Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. *Arthritis Rheum.* 54(11), 3399–3407 (2006).

3 Pincus T, Sokka T, Kautiainen H: Further development of a physical function scale on a MDHAQ [corrected] for standard care of patients with rheumatic diseases. *J. Rheumatol.* 32(8), 1432–1439 (2005).

4 Hyrich KL, Watson KD, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register: Predictors of response to anti-TNF-α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)* 45(12), 58–65 (2006).

5 Karlsson JA, Kristensen LE, Kapetanovic MC, Gülfe A, Saxne T, Geborek P: Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford)* 47(4), 507–513 (2008).

6 Gomez-Reino JJ, Carmona L; BIOBADASER Group: Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Res. Ther.* 8(1), R29 (2006).

7 Hjardem E, Østergaard M, Pødenphant J *et al.*: Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor α inhibitor? *Ann. Rheum. Dis.* 66(9), 1184–1189 (2007).

8 Kristensen LE, Saxne T, Nilsson JA, Geborek P: Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. *Arthritis Res. Ther.* 8(6), R174 (2006).

9 Kristensen LE, Kapetanovic MC, Gülfe A, Söderlin M, Saxne T, Geborek P: Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford)* 47(4), 495–499 (2008).

10 Ostergaard M, Unkerskov J, Linde L *et al.*: Low remission rates but long drug survival in rheumatoid arthritis patients treated with infliximab or etanercept: results from the nationwide Danish DANBIO database. *Scand. J. Rheumatol.* 36(2), 151–154 (2007).

11 Zink A, Listing J, Kary S *et al.*: Treatment continuation in patients receiving biological agents or conventional DMARD therapy. *Ann. Rheum. Dis.* 64(9), 1274–1279 (2005).

12 Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ; British Society for Rheumatology Biologics Register: Outcomes after switching from one anti-tumor necrosis factor α agent to a second anti-tumor necrosis factor α agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum.* 56(1), 13–20 (2007).

13 Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T: Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor α inhibitor infliximab. *Arthritis Rheum.* 54(12), 3782–3789 (2006).

14 van der Laken CJ, Voskuyl AE, Roos JC *et al.*: Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. *Ann. Rheum. Dis.* 66(2), 253–256 (2007).

15 Gülfe A, Kristensen LE, Geborek P: Six and 12 weeks treatment response predicts continuation of tumor necrosis factor blockade in rheumatoid arthritis: an observational cohort study from southern Sweden. *Rheumatology (Oxford)* (2009) (In press).

16 Maxwell JR, Potter C, Hyrich KL *et al*; Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate: Association of the tumour necrosis factor-308 variant with differential response to anti-TNF agents in the treatment of rheumatoid arthritis. *Hum. Mol. Genet.* 17(22), 3532–3538 (2008).

17 Potter C, Hyrich KL, Tracey A *et al.*: Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. *Ann. Rheum. Dis.* 68(1), 69–74 (2009).