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Editorial

If You Want to Perform a Cost-effectiveness Trial, First Do a Modeling Study

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Rheumatoid arthritis (RA) has become an expensive disease to treat with the introduction of biological therapies in the early 2000s. Therefore, it is of crucial importance that researchers, together with clinicians, search for treatment strategies with the best value for money. That is why we would like to thank the authors of the paper entitled, "Effect on Costs and Quality-adjusted Life-years of Treat-to-target Treatment Strategies Initiating Methotrexate, or Tocilizumab, or Their Combination in Early Rheumatoid Arthritis," published in this issue of *The Journal of Rheumatology*, for their honorable attempt[1].

The authors describe the results of a preplanned cost-effectiveness analysis as a follow-up on the publication of the primary results of the U-Act-Early trial[2]. This trial was a 2-year, randomized, double-blind, double-dummy, strategy study at 21 rheumatology outpatient departments in the Netherlands, in which 3 treatment strategies were compared: start tocilizumab (TCZ) plus methotrexate (MTX); TCZ plus placebo-MTX (the TCZ arm); and MTX plus placebo-TCZ (the MTX arm). The primary results of the U-Act-Early trial showed a better immediate initiation of TCZ with or without MTX over initiation of MTX alone, but this difference had disappeared after 2 years due to tight control of disease activity in combination with active tapering during the trial, which resulted in comparable TCZ use at study end.

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In their current paper[1], the authors hypothesized that initiating a TCZ-based strategy for patients with early RA using a strict treat-to-target approach and including a clear tapering strategy when in sustained remission, might become cost effective. They were not able to confirm this hypothesis, as they found that estimated from a societal perspective, TCZ + MTX compared to MTX is more expensive and only slightly more effective, whereas there is also a 23% chance that it is less effective [loss in quality-adjusted life-years (QALY)]. This resulted in a mean incremental cost-effectiveness ratio of €594,021 per QALY, which is well beyond the maximum willingness-to-pay value of €80,000 per QALY gained in the Netherlands or £30,000 in the UK.

The fact that TCZ was tapered in patients who achieved sustained remission, which is in line with the idea that earlier remission leads to earlier tapering, lowers the costs for the TCZ strategies. Although it was not a formal part of the original trial strategies to taper TCZ, it apparently happened frequently in daily clinical care. Therefore, the cost and effectiveness estimations in this arm should rather well represent current standard of care when using biologic disease-modifying antirheumatic drugs (bDMARD) in the treatment of RA.

Remarkably, the use of initial oral or parenteral glucocorticoids (GC; prednisone or methylprednisolone) was not part of treatment algorithms and were, by protocol, not even permitted during the first 3 months of the study. However, the European League Against Rheumatism (EULAR) recommendations[3] on the treatment of RA have already included short-term GC use when initiating or changing conventional synthetic DMARD (csDMARD) since 2012, predating the design of U-Act-Early. Therefore, one could assume that the effectiveness of the MTX monotherapy arm in the U-Act-Early trial is a less-than-optimal, state-of-the-art treatment. Following this line of reasoning, one could assume that a comparator arm following usual care as recommended (combination of MTX with oral GC) would lead to better effectiveness in the usual care arm and less TCZ use in

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this arm, favoring the incremental costs-effectiveness ratio even less. Nonetheless, the results of the U-Act-Early trial add to the notion that the current EULAR state-of-the-art RA treatment strategy is indeed very hard to improve upon.

Another remarkable result presented in the paper by Verhoeven, *et al*[1] is that when comparing TCZ monotherapy to MTX monotherapy, the costs related to productivity loss measured over 5 years are lower in the TCZ monotherapy group, and positively influence the mean incremental costs. The authors hypothesize that omitting MTX may be an advantage in terms of effects on productivity, since MTX is associated with mild adverse events. However, this reasoning is not concordant with the chance that this strategy will result in QALY loss, which is estimated to be 65%. In this light, a comparison between TCZ + MTX versus TCZ monotherapy could be valuable, but remarkably, this comparison is not presented in the paper.

All in all, could we say that the treatment strategies implemented in the U-Act-Early trial could have been designed more optimally, and that in the cost-effectiveness analysis, other comparisons would also have been relevant? This seems especially valid when considering that many strategy studies in the field of RA seem to show that strategies have the same results after 1 or 2 years, when escalation and tapering of treatment based on tight control of disease activity are also incorporated. This statement is again being confirmed by the recently published data from the NORD-STAR trial, also showing short-term noninferiority of MTX-based conventional DMARD strategy when combined with GC compared to 3 different biologics-based (combined with MTX) strategies[4]. When assuming that over a longer period, the effectiveness of the strategies will be equal, one can calculate on the back of an envelope that a csDMARD strategy will be the least expensive and thus preferred. The fact that U-ACT-Early was sponsored by a pharmaceutical company might have made making all design choices optimal from a clinical perspective somewhat complicated, although the NORD-STAR trial[4], also a pharmaceutical company–sponsored study, demonstrates nicely that it is not impossible to align the interests of both the scientific and commercial communities with commercial parties.

The more scientific approach to such a back-of-the-envelope calculation is a cost-effectiveness modeling study, which is a mathematical framework that facilitates estimation of the consequences of a healthcare decision. A model can be used to combine existing knowledge from literature or research databases on the effectiveness of different treatment options to estimate the potential effectiveness and costs over a predefined time horizon. Combined with interviews about daily clinical practice that may feed the structure of the model, increasing its face validity, modeling can be a very valuable tool. Modeling is being used in the field of rheumatology to also estimate the cost effectiveness of treatment strategies in early RA. An example is the study published by Schipper, *et al* in 2011 that starting with MTX or tumor necrosis factor inhibitors (TNFi) was expected to have similar effectiveness over a period of 5 years and due to the much higher price of initial TNFi, this would not be cost effective[5].

How should such a cost-effectiveness model look like in the field of rheumatology? A Markov model could be used to compare treatment strategies that are relevant for clinical practice and that represent current clinical guidelines. A Markov model consists of mutually exclusive states, wherein hypothetical patients transfer from state to state in each predefined period (called *cycle time*). These states could be defined by, for instance, Disease Activity Score in 28 joints (DAS28) categories; such a model has been validated and published by Welsing, *et al*[6]. Costs and quality of life (QOL) values (utilities) are related to these states, in which being in a higher DAS28 state generates higher costs and lower QOL. Literature or research databases can be used to estimate probabilities for tranferring from state to state for the hypothetical patients in the different treatment strategies. In the analyses, all information is being combined into an estimation of the incremental cost effectiveness of a potential new strategy compared to the first best alternative, often being usual care.

In the case of the treatment of patients with early RA, state-of-the-art care is a strategy with initial MTX combined with oral corticosteroid (tapered quickly). When a tight control of disease activity shows nonresponse, bDMARD can be added. From the cost point of view, TNFi for which biosimilars are available, or rituximab (RTX) are preferred. When estimating the potential cost effectiveness of newer biologics as initial therapy, a strategy with an initial biosimilar TNFi or RTX might also be used as comparator. We would recommend including active tapering of treatment in case of sustained remission as part of the treatment strategy. Cost effectiveness of new strategies could be hypothesized when you assume better effectiveness in terms of achieving remission in the short term and attaining (drug-free) remission in long term.

How could a modeling exercise before designing a trial influence your choices? The model can be used to do threshold analyses, for instance, on how effective the new strategy should be in order to trade off the extra costs related to the strategy, from a medical as well as a societal perspective (including loss of work participation). Another benefit would be to determine how low the price of a new drug should drop (e.g., with the introduction of a biosimilar) before becoming cost effective. These thresholds should be presented to experts with the question of whether it might be realistic. A negative answer on this question could, and in fact should, result in not performing the trial. An additional way to use a model is by searching for subgroups of patients, for instance, those with high disease activity, in which the chance of the new strategy being cost effective is the highest. This could result in a trial being performed only in such a subgroup. To summarize, a model can be used to generate sensible and clinically relevant hypotheses that can then be confirmed or rejected in a well-designed trial.

In conclusion, we very much appreciate the efforts of Verhoeven, *et al*[1] for their work on this interesting strategy study; however, the study also made it clear that if you want to do a relevant cost-effectiveness trial, you must first do a modeling study.

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