The Journal of Rheumatology 2021;48:1771–3
doi:10.3899/jrheum.201510
First Release May 15 2021

The Journal of Rheumatology

Editorial

Unravelling the Cost of Biological Strategies in Rheumatoid Arthritis: A Kaleidoscope of Methodologies, Interpretations, and Interests

Johannes W.G. Jacobs[1], Maxime M.A. Verhoeven[1], and Paco M.J. Welsing[1]

In this issue of *The Journal of Rheumatology*, Müskens, *et al* describe the effect of the introduction of an etanercept (ETN) biosimilar on antirheumatic medication cost[1]. After a Dutch rheumatology department launched this biosimilar as a substitute for the more expensive biologic ETN, the accumulated 3-monthly antirheumatic medication cost in that hospital pertaining to in- and outpatients with rheumatoid arthritis (RA), mainly consisting of cost of biologic disease-modifying antirheumatic drugs (bDMARD), decreased, as expected. However, this financial advantage was lost within less than a year, due to an increase of the percentage of the patients with RA treated with a bDMARD. This means that the potential savings of using the biosimilar were spent on extra patients treated with a bDMARD, although the rheumatologists had not formally changed their bDMARD prescription policy. The brisk increase in percentage of patients treated with a bDMARD in this time period is not compatible with the general trend of slowly increasing bDMARD use over time.

Should the reader of the paper[1] thus conclude that introduction of cheaper biosimilars is not effective in reducing medication cost in the longer term? Our answer would be that interpretations of this, and of any costing study, strongly depend on what we are looking at, how we are looking, and who is looking.

[1]*J.W. Jacobs MD, PhD, Associate Professor, M.M. Verhoeven, MSc, P.M. Welsing, PhD, University Medical Center Utrecht, Utrecht, the Netherlands.*

The authors declare no conflicts of interest.

Address correspondence to Dr. J.W. Jacobs, Department of Rheumatology & Clinical Immunology, G02.228, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands. Email: j.w.g.jacobs-12@umcutrecht.nl.

What we are looking at: Treatment strategy

Müskens, *et al*[1] found no statistically significant difference in disease activity in those starting a biological before the biosimilar introduction (mean Disease Activity Score assessing 28 joints [DAS28] 4.7), versus in those starting a bDMARD after the biosimilar introduction (DAS28 4.5). Notably, the mean age of patients at the start of bDMARD after the biosimilar introduction was statistically significantly higher than that before the biosimilar introduction (58 vs 52 yrs, respectively). After the biosimilar introduction, the percentage of bDMARD patients concomitantly using methotrexate (MTX) dropped from 68 to 54. The most plausible explanation seems to be that after the introduction of the cheaper biosimilar, the rheumatologists in this center felt freer to initiate bDMARD, also in elderly patients with adverse effects of MTX, to allow for stopping MTX.

The question then arises whether this increased use of bDMARD and the resulting loss of financial benefit would also have occurred if stricter guidelines on bDMARD initiation and usage (e.g., on concomitant MTX usage and dose) had been applied. Perhaps the main conclusion of the Müskens, *et al* paper[1] is that persistent financial benefit in their study would have required more stable adherence to their prescription policy.

The study of Müskens, *et al*[1] can be regarded as a budget impact analysis (i.e., an economic assessment that estimates the financial consequences of adopting a new intervention), but one that analyzed only medication cost, not financial consequences (e.g., of the intervention's effect on frequency of clinical visits and admissions). Moreover, not only the (medication) cost perspective but also the clinical perspective is relevant. What were the clinical effects of treating the extra patients with a bDMARD? Could the potential savings of using the biosimilar not more (cost-)effectively have been spent on another treatment

See Bending the cost curve, *page 1803*

strategy? Take, for instance, a strategy in early RA, wherein as first medication, a bDMARD (preferably a biosimilar) is initiated concomitantly with MTX, with the target of drug-free remission, hence the intended use of the bDMARD is for a limited time only (thus reducing medication cost). This seems an attainable goal, given the results of the U-Act-Early trial[2]. In this study, approximately 30% of the patients with early RA who started with a bDMARD (tocilizumab [TCZ]) as first treatment (two strategy arms, one with and one without MTX concomitantly) shortly after diagnosis achieved this target, whereas this was only 10% in the strategy arm initiating MTX as first treatment[2]. The cost-effectiveness analysis of the 2-year U-Act-Early trial and its 3-year posttrial follow-up period, during which treatment was according to the decision of the rheumatologist[3], showed that the strategies of initiating TCZ as first-line therapy in early RA were not cost effective over the 5 years, compared to the strategy initiating MTX and adding TCZ later on, if indicated. Possible explanations are the finding that bDMARD use in the strategy arms during the study period became more similar as a consequence of the strict treat-to-target strategy, and the lack of tapering during the nonprotocolled follow-up period[4]. Again, this underlines that for strategies aiming to save costs or improve cost effectiveness, clear recommendations on the use and strategy of expensive DMARD are needed and have to be adhered to. In this cost-effectiveness study of the U-Act-Early trial and follow-up period, selecting a prognostically unfavorable subgroup based on DAS28 and the Health Assessment Questionnaire notably improved cost effectiveness. This suggests that it remains essential for rheumatology communities to continue developing novel strategies with bDMARD in RA, to reduce cost and improve long-term effectiveness.

How we are looking: Methodology of costing studies

Müskens, *et al*[1] performed a quasi-experimental (before-after) study and data were collected in daily practice, appropriate to study real-world effects. However, only medication cost for RA was analyzed, and only in 1 hospital, which is a rather limited scope. A justification is that in the Netherlands, bDMARD are paid for and delivered by the hospital (outpatients collect their bDMARD medication, if to be self-administered subcutaneously, at the hospital pharmacy). Discounts on the maximal governmentally set bDMARD purchase prices are negotiated by each individual hospital (or collaborative hospital group) with the pharmaceutical companies. The percentage of the bDMARD cost that is reimbursed to the hospital (groups) by the health insurance organizations is negotiated between these two parties (see Figure)[5]. This intricate system explains the interest of individual Dutch hospitals in the number and cost of bDMARD prescribed in their center. As such, the results of the paper of Müskens, *et al*[1] are important. However, the negotiated prices of biologics are not made available publicly, and these, and not the publicly known reference prices (i.e., the nonnegotiated prices) were used in the analyses of Müskens, *et al*[1,6]. This hampers the generalizability of the results of this study in a single center. Interestingly, after the introduction of biosimilars in the Dutch market in 2015, the mean purchase price of ETN for Dutch hospitals decreased by almost 60%, reducing the price difference between ETN and its biosimilar[5].

As mentioned above, the study of Müskens *et al*[1] only analyzed costs that are relevant for a certain budget, and is therefore classified as a budget impact analysis. For a more comprehensive evaluation of treatment strategies, health economic studies are more appropriate. Depending on which costs and outcomes are taken into account in the analysis, an economic evaluation can be classified as a cost-effectiveness (weighing costs against a disease-specific health outcome), cost-utility (weighing costs against a general quality of life [QOL] "utility" measure; i.e., quality adjusted life-years [QALY]), cost-minimization (only analyzing cost, assuming equal effectiveness and similar populations; this condition was not met in the Müskens, *et al* study[1]), or cost-benefit (expressing health outcomes also in monetary value, leading to a net monetary effect) analysis. Health economic studies of medication strategies often are cost-effectiveness or cost-utility analyses.

In all analyses, key decisions are on which costs specifically to include. First, there are costs within the healthcare sector (i.e., related to intervention, not only cost of medication, but for instance also of intravenous administration[4], testing for latent tuberculosis, physician visits and consultations, and admissions)[7]. Second, there are patient and family costs, occurring outside of the healthcare system, such as care provided by family members, and transportation[7]. Third are the costs in other sectors, such as those related to loss of productivity due to work disability, absenteeism (time missed from work due to health reasons), and presenteeism (impaired performance while at work due to health reasons, resulting in productivity loss)[7,8]. This last cost category is often referred to as indirect cost. Cost of work disability can be estimated by applying the human capital method, taking into account productivity loss over the whole period of the potential working life, or by the friction-cost method. Herein, only the average timespan the employing organisation needs to restore the initial production level is taken into account[7].

Next, the choice of the measure of effectiveness is of interest. This may be a unidimensional and disease-specific health outcome (e.g., the percentage of patients achieving remission), but it may also be a multidimensional, generic health outcome, such as QALY. Generic health outcomes enable comparisons of outcomes of studies evaluating quite different interventions[7].

If Müskens, *et al*[1] had performed a longer-term study with a wider scope that also looks at indirect cost, their study might have had a positive result (for example, the higher percentage of RA patients using a bDMARD could have led to higher levels of QOL and lower levels of productivity loss in the investigated RA population).

Who is looking: Interests and interpretations of specific stakeholders

Interpretations of whether an expensive medication or novel therapeutic strategy is "worth it" depend not only on the methodology used (i.e., costs and outcomes assessed) but also on the eye of the beholder (i.e., stakeholder; see Figure). Of course, their interests also determine choices in study design and methodology. For a Dutch hospital, financial data on prescribed bDMARD for in- and outpatients, including biosimilars, are

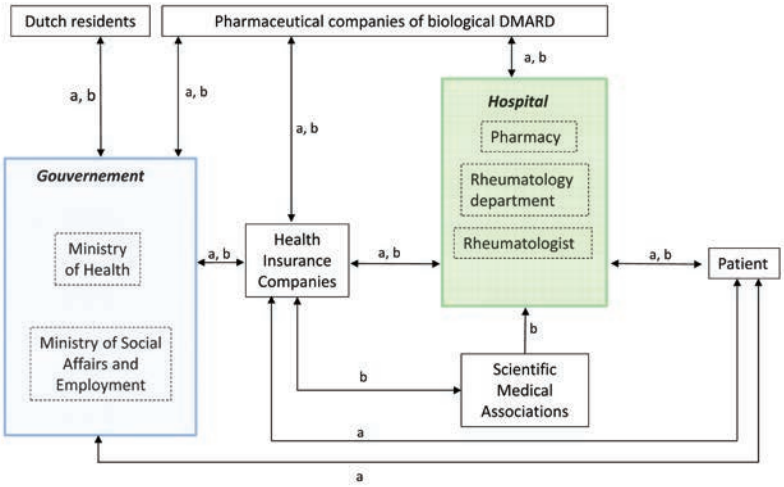

Figure. The interplay of financial associations, guidelines, and agreements between Dutch stakeholders of biological disease-modifying antirheumatic drug therapy. This nonexhaustive model, based specifically on the Dutch situation, serves only as an example; for each country, situations will differ. Each stakeholder might be inclined to look at results of analyses specifically suited to their situation. a: financial interactions. b: agreements, guidelines, nonfinancial interactions. Within each colored rectangle, several interrelations of type a and b exist.

relevant. This would be different for hospitals in other countries, where bDMARD for outpatients are not paid by the hospital, or where bDMARD prices are set per region or the entire country and all medication costs are reimbursed by their National Health Service system[9,10].

For patients with RA, if they do not have to pay extra (i.e., beyond their health insurance) for the medications, the QOL and antidisability effects of bDMARD strategy studies are the most relevant. For Ministries of Health, control of the health budget, especially for the duration of their administrations, is important, and the results of budget impact analyses will likely be of most interest. For the government as a whole, as well as for the tax-paying population, comprehensive cost-utility studies also incorporating indirect cost would be important. However, it is difficult to take all possible gains in indirect costs resulting from increased adequate use of bDMARD by patients with RA into account in these analyses, given the difficulty in estimating the reduction of expenditures from unemployment, absenteeism, and moreso from presenteeism. Also, a longer time period (often many years) is necessary for these gains in indirect costs to be fully assessed.

In conclusion, Müskens, *et al*[1] are to be complemented with their study on real-world medication cost with relevant results for a Dutch hospital. The authors report a negative study result. However, their study might have had positive results if there would have been a more stable bDMARD prescription policy, and more importantly, if it would have had a broader scope, such as that of a health economic evaluation, and if it would have analyzed novel treatment strategies with a biosimilar.

REFERENCES

1. Müskens WD, Rongen-van Dartel SA, van Riel PL, Adang EM. Does Etanercept biosimilar prescription in a rheumatology center bend the medication cost curve? J Rheumatol 2021;48:1803-9.
2. Bijlsma J, Welsing P, Woodworth T, Middelink L, Pethö-Schramm A, Bernasconi Corrado, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet 2016;388:343-55.
3. Verhoeven MM, Tekstra J, Welsing PMJ, Borm ME, Bruyn GA, Bos R, et al. Effectiveness and safety over 3 years after the 2-year U-Act-Early trial of the strategies initiating tocilizumab and/or methotrexate. Rheumatology 2020;59:2325-33.
4. Verhoeven MM, Tekstra J, van Laar JM, Pethö-Schramm A, Borm ME, Bijlsma JW, et al. 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. J Rheumatol 2020 Nov 1 (E-pub ahead of print).
5. Authority for Consumers and Markets. TNF-alpha inhibitors sector inquiry. 2019. [Internet. Article in Dutch. Accessed November 21, 2020.] Available from: www.acm.nl/sites/default/files/documents/2019-09/sectoronderzoek-tnf-alfaremmers.pdf
6. Zorginstituut Nederland. [Internet. Accessed November 21, 2020.] Available from: www.medicijnkosten.nl
7. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015: 464.
8. Escorpizo R, Bombardier C, Boonen A, Hazes JMW, Lacaille D, Strand V, et al. Worker productivity outcome measures in arthritis. J Rheumatol 2007;34:1372-80.
9. World Health Organization Regional Office for Europe. Medicines reimbursement policies in Europe. [Internet. Accessed November 21, 2020.] Available from: www.euro.who.int/__data/assets/pdf_file/0011/376625/pharmaceutical-reimbursement-eng.pdf
10. Putrik P, Ramiro S, Kvien TK, Sokka T, Uhlig T, Boonen A, et al; Equity in Clinical Eligibility Criteria for RA treatment Working Group. Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? Ann Rheum Dis 2014;73:2010-21.