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ORIGINAL RESEARCH
Economic Evaluation

The Comparison of Trial Data–Based and Registry Data–Based Cost-Effectiveness of Infliximab Treatment for Rheumatoid Arthritis in Sweden Using a Modeling Approach

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ABSTRACT

Objective: To evaluate the precision of the predictive cost-effectiveness assessment based on a phase 3 clinical trial with infliximab for the treatment of rheumatoid arthritis in Swedish clinical practice. **Methods:** Three patient cohorts were identified: the patients included in the infliximab trial (ATTRACT), patients initially treated with infliximab from a Swedish registry (STURE), a subset of these registry patients meeting inclusion criteria for the ATTRACT trial was the third patient cohort; two sets of assumptions in relation to the efficacy data were evaluated: "ATTRACT" (efficacy data over the duration of the trial) and "STURE" (effectiveness data over 10 years). In addition, the impact of including the placebo effect for the comparator was evaluated as a basis for the calculation of cost-effectiveness by using a modeling approach. A health economic model was utilized to estimate the cost per quality-adjusted life-year (QALY) gained. **Results:** The results for the three patient cohorts ranged from cost saving to a cost per QALY gained of €2,400 and €24,900 to €26,000 when the ATTRACT and STURE assumptions were used, respectively. Sensitivity analyses indicated that the inclusion of placebo effect had the largest effect on the results, increasing the cost per QALY gained to approximately €50,000 for all patient cohorts. **Conclusions:** The treatment effect of infliximab measured in clinical trials and clinical practice results in comparable cost-effectiveness ratios, as calculated by using a modeling approach, whereas the assumptions made in relation to the effectiveness data and the chosen comparator have a large impact on the results. This reinforces the value of early modeling studies based on randomized clinical trial data, but assumptions made need to be carefully assessed.
Keywords: cost-effectiveness analysis, randomized clinical trial, rheumatoid arthritis.

Introduction

At the time of reimbursement decisions for new interventions, cost-effectiveness analyses have to be based on clinical trial data and assumptions regarding future treatment patterns. To ensure internal validity, and most often because of lack of appropriate data, the placebo arm from the randomized clinical trial (RCT) is generally used as the comparator. The precision of these cost-effectiveness models can, however, seldom be rapidly verified with clinical practice data, as frequently the patients treated first with a new technology are the most severe cases and thus not always comparable to the RCT patients [1]. The ability of such models to predict the cost-effectiveness of the evaluated treatment in clinical practice is also debated because the controlled nature, short time, and patient selection of the RCT do not cohere with a decision model [2]. In addition, Philips et al. [3] argue that it is not reasonable to assume that such a model will predict the future accurately because it can only incorporate the data available at the time of conducting the analyses. On the same note, Weinstein et al. [4] highlight that predictive validation is reasonable only when there is consistency of structure over time, which is seldom the case in health care. Nevertheless, although a predictive validation of the actual model may be of limited interest, it is of greater interest from both a methodological and an investment perspective to evaluate the impact of using clinical trial data when making decisions about treatments in clinical practice. Do the highly selected patient population from a clinical trial provide a good estimation of the health economic outcomes in clinical practice? What lessons can be learned to make more precise projections in future evaluations? In recent years, drug reimbursement agencies have also increasingly emphasized the necessity of follow-up studies based on real-world evidence from clinical practice to facilitate reevaluation of funding and positioning of treatments.

An area in which it is possible to perform such a predictive validation of an early clinical trial assessment is for the cost-effectiveness of biologic treatments for rheumatoid arthritis

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(RA) in Sweden. Biologic treatments (tumor necrosis factor [TNF] inhibitors) have been available in Sweden for more than 10 years, and patients are carefully followed in registries, providing an opportunity to assess the cost-effectiveness of these treatments in clinical practice. It has previously been estimated that a large proportion, if not the majority, of the patients treated with TNF inhibitors in clinical practice would not be eligible for inclusion in the clinical trials [5,6]. It is therefore of interest to assess whether treating a different patient group in clinical practice has an impact on the estimated health economic consequences compared with prior assessments of these treatments.

In this study, we evaluated the predictive validity of cost-effectiveness models based on trial data in comparison to models based on registry data, using the example of infliximab (INF). This was the first anti-TNF introduced in Sweden, and there are currently cost-effectiveness assessments based on both clinical trial data [7,8] and data from clinical practice [9] available, using similar models. The difference in the effectiveness of INF therapy between RCT and clinical practice has previously been studied, although not addressing the full health economic consequences of the different patient cohorts. The previous studies have instead contributed with enhanced knowledge of differences in Americal College of Rheumatology (ACR) response [5,6] and gain in quality-adjusted life-years (QALYs) in the initial year of treatment [10] between the cohorts included in the clinical trial and treated in clinical practice.

An early cost-effectiveness model based on the pivotal RCT (ATTRACT) was published at the time of introduction [7,8], and the model was updated by using data from the Stockholm biologics registry (STURE) for the reevaluation of the use of biologics in RA in Sweden [9]. In addition to the difference in the patient material, the two evaluations used somewhat different assumptions in relation to the effectiveness data in the health economic models. The objective of this study was thus to evaluate the impact on the cost-effectiveness results of using effectiveness estimates from different patient cohorts from clinical trial and clinical practice as well as to explore which assumptions related to the effectiveness data (including comparator) most influence the cost-effectiveness results. The impact of other model assumptions or model development over time was not examined within the scope of this article. For comparability, a similar method for matching patients from clinical practice to the RCT cohort as used in previous studies [5,6] is proposed in this current assessment.

Methods

To assess the impact of different effectiveness data and the assumptions made in relation to these data, the following steps were taken:

1. Identifying a suitable analytical framework: A previously validated Markov model was used to estimate the cost per QALY gained.
2. Identifying effectiveness data and populating the model: The data investigated were retrieved from an RCT and a registry, providing three cohorts for comparison.
   i. An RCT-based cohort
   ii. A registry-based cohort
   iii. A registry-based cohort with patients matching the RCT cohort in terms of disease criteria (“matched cohort”)
3. Identifying assumptions in relation to the effectiveness data that may influence the results: As this is based on two previously published health economic assessments, two sets of assumptions were identified, necessitated by the different nature of the two data sources.
   i. RCT-based assumptions
   ii. Registry-based assumptions
4. Performing analyses of a two-dimensional base case (three cohorts in two sets of assumptions) and different alternative scenarios to identify the drivers of the results. Probabilistic sensitivity analyses (PSAs) were used to assess the precision of the base-case scenario.

Analytical Framework

A cost-effectiveness model is needed to enable an evaluation of the impact of any data in health economic terms. A previously validated cost-effectiveness model of TNF-inhibitor treatment [7,9,11] was therefore used for the computation of the cost per QALY gained from treatment. By changing the patient cohort and assumptions around the effectiveness data in the model, the impact of these factors on the cost-effectiveness results was assessed.

The model used for this assessment was a previously validated Markov cohort model programmed in TreeAge, originally developed for the cost-effectiveness assessment of INF based on the ATTRACT trial [7,8]. The model has thereafter been updated in other publications of TNF-inhibitor treatments [9,11], and the updated version was used for this current assessment. The current model has five health states based on functional status measured with the Health Assessment Questionnaire (HAQ) (cutoffs at 0.6, 1.1, 1.6, and 2.1), whereas the original model had six HAQ states (states five and six combined into one in the updated version). The updated model also includes a dimension of high and low disease activity (cutoff at Disease Activity Scale [DAS28] 3.2) to each HAQ state, which was not present in the original version. The model runs in annual cycles for a time frame of 10 years. In each cycle of the model, patients can transit to other health states (HAQ or DAS28), remain in the current health state, or die. There is also a probability of discontinuing TNF-inhibitor treatment in each cycle, and after discontinuation, patients remain off treatment for the remainder of the simulation. The TNF-inhibitor treatment evaluated is compared with a scenario of no biologic treatment (either with or without placebo effect). A simplified schematic picture of the model is presented in Figure 1. The model was populated with data on direct and indirect costs stratified by HAQ category and utilities stratified over HAQ categories and disease activity, in line with the publication of the STURE model [9,11]. The results are presented in €2009-year values, presented for the societal perspective of Sweden.

Patient Cohorts

The effect of using effectiveness data from clinical trials and clinical practice data was explored by assessing the impact on

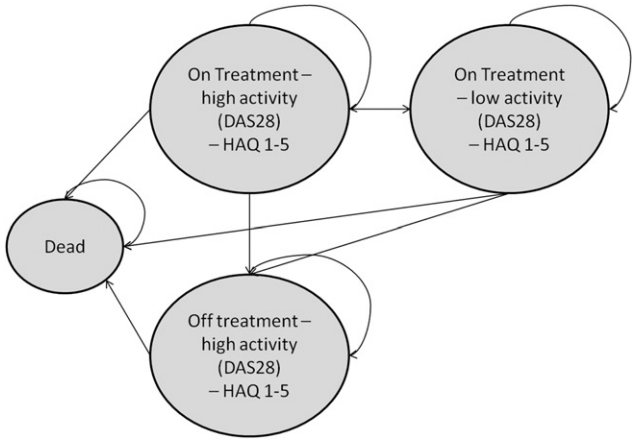

Fig. 1 – Simplified model structure.