COST-EFFECTIVENESS EVALUATION OF TOCILIZUMAB IN ROMANIAN HEALTH CARE SYSTEM

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The aim of the study is to evaluate cost-effectiveness of tocilizumab in Romania for the treatment of Rheumatoid Arthritis in patients with traditional DMARD inadequate response (DMARD-IR).

Methodology compares two alternatives: sequence of treatment including either infliximab, etanercept or adalimumab, followed by rituximab, and sequence of treatment including tocilizumab as first agent in the treatment sequence, followed by rituximab. Data used is from clinical trials, and also local cost data for direct and indirect costs of treatment sequences. Time horizon is life-time period of each individual.

The type of evaluation is cost-utility, and the perspective is that of the payer (National Health Insurance House) as well as of the society. The Incremental Cost-Effectiveness Ratio is 58,866 Rol per QALY gained, which compares favorably with other treatments reimbursed by the National Health Insurance House. Results were tested using a one-way sensitivity analysis.

Keywords: cost-effectiveness analysis, rheumatoid arthritis, treatment using tocilizumab.

Background

Prevalence of Rheumatoid Arthritis (RA) is estimated in between 0.5%-1% of the population in European countries (NICE, 2006). Consequently, this translates into approximately 200,000 cases of RA in Romania. In 2008 in Romania 20,000 patients were hospitalized for RA (SNSPMS, 2008).

For the treatment of RA, the most commonly prescribed first-line traditional disease-modifying anti-rheumatic drugs (tDMARDs) are methotrexate and sulphasalazine. After inadequate response, patients may switch to another tDMARD alone (leflunomide, gold, azathioprine, hydroxychloroquine, or ciclosporine), a combination of tDMARDs, or to a biologic DMARD (bDMARD). The latter group includes anti-tumour-necrosis-factor alpha (anti-TNFα) therapies (etanercept, infliximab, and adalimumab), rituximab and abatacept. After failure on a bDMARD therapy, patients may switch back to previously untried tDMARDs. Eventually, a patient may exhaust these and then receive palliative care. Joint replacement is also an option.

Tocilizumab (RoActemra®) is a new humanised interleukin-6 (IL-6) receptor monoclonal antibody with a novel mechanism of action providing a unique treatment option for RA. The results of four phase III clinical trials demonstrate a significant reduction in the signs and symptoms of the disease, making tocilizumab a promising alternative for RA patients.

Next we present the methodology used to assess cost-effectiveness of tocilizumab in the treatment of rheumatoid arthritis for patients with DMARD inadequate response (DMARD-IR) and the results regarding cost-effectiveness of therapy sequence including tocilizumab.

Cost-effectiveness evaluation is based on a pharmaeconomics model – Actemra Cost-Effectiveness model (ACE) - developed by THEMA Research Limited for F. Hoffman-La Roche. The model has a number of characteristics which are presented as part of the study methodology.

Metodology

There is no cost-effectiveness study on tocilizumab published to date. This study is aimed to evaluate the cost-effectiveness of tocilizumab where two alternatives are compared, representing two different treatment sequences:

- sequence of treatment excluding tocilizumab, which is the current standard care including either infliximab, etanercept or adalimumab, followed by rituximab;
- sequence of treatment including tocilizumab, where tocilizumab is used as first agent in the treatment sequence, followed by rituximab.

For the purpose of comparison of costs and effectiveness of both alternatives, it was necessary to first identify the most used biological in the treatment sequence of patients with RA with traditional DMARD inadequate response (DMARD-IR), and anti-TNFα inadequate response (TNF-IR), in current Romanian medical practice.
Data regarding use of biological treatments was obtained by means of a questionnaire and discussions with an expert panel of rheumatologists. The questionnaire contained questions regarding the usual therapy in RA patients, the use of biological treatment, as well as resource utilization (biological drugs, other associated drugs to the therapy, other services). The biological drugs currently in use in Romania are infliximab, etanercept, adalimumab and rituximab. Data collected indicated infliximab as the most frequent biologic agent in Romanian current practice, followed by rituximab when inadequate response to one or more anti-TNFs. The anti-TNFs cycling in Romania is not common, a local RA market study estimated in 2008 the switch rate for a second anti-TNF at 8% (IMS, 2008). The two alternatives selected for comparison are presented in Table 1.

**Table 1. Alternatives for comparison in cost-effectiveness evaluation of tocilizumab**

<table>
<thead>
<tr>
<th>Sequence excluding tocilizumab</th>
<th>Sequence including tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Infliximab</td>
</tr>
<tr>
<td>Rituximab (TNF-IR)</td>
<td>Rituximab (TNF-IR)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Leflunomide</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Palliative care</td>
<td>Palliative care</td>
</tr>
</tbody>
</table>

**Source of data:** Study on cost-effectiveness evaluation of the treatment using tocilizumab, Roche Romania

The primary outcome of the economic evaluation is cost per quality adjusted life-years gained (QALYs). The model calculates a cost-effectiveness ratio of a standard treatment sequence for RA patients versus an alternative treatment sequence for RA patients where tocilizumab is the initial agent in the sequence.

**Type of economic evaluation:** Cost-utility

The model assumes that patients enter the process when inadequate response to the first line treatment is established. Costs and effects are estimated from this point onward.

**Evaluation of costs and effectiveness**

Effectiveness of using tocilizumab as first agent in treatment sequence of RA patients with DMARD inadequate response is measured for a pooled DMARD-IR patient population. Results in the model are simulated for 10,000 patients. The model assumes that patients enter the process when inadequate response to the first line treatment is established. Costs and effects are measured and calculated from the perspective of the patient.

**Model Populations**

Population matches characteristics of those of patients of four Phase III tocilizumab clinical trials (OPTION, TOWARD, LITHE & RADIATE); data is used for pooled DMARD-IR population. Results in the model are simulated for 10,000 patients. The model assumes that patients enter the process when inadequate response to the first line treatment is established. Costs and effects are estimated from this point onward.

**Evaluation of costs**

Evaluation of costs is based on the following assumptions and calculations:

- median time on treatment with a biologic (infliximab) for a patient with RA is 39 months, i.e 3.25 years (Brock et al. 2007) and an average time on treatment with tocilizumab is 3.25 years; treatment consequences are evaluated during lifetime period of patients.

- The costs involve treatment and post-treatment costs, and they are considered for the lifetime period of patients.

- Type of costs considered: direct costs of therapy (direct medical, direct non-medical: administration and monitoring costs) and indirect costs (estimated loss of productivity).

- For direct non-medical costs estimation (administrative and monitoring costs) data on resources utilization (drugs, associated drug therapy and services) was collected from experts though the questionnaire; according to experts, the most frequently used biologic in Romanian practice is infliximab.
Results on costs are discounted by 6%; no discount was applied to effects. This is consistent with other evaluations in Romanian setting, where same rates were applied.

For testing of results, a one-way deterministic sensitivity analysis was performed, by varying the cost discount rate from 6% to 3.5%.

The Direct cost of therapy is determined as sum of the acquisition cost of drugs, the administration cost and monitoring cost of drugs when patient is under treatment.

The acquisition cost of drugs is the maximal retail price for drugs from the National Catalog of Drugs (CANAMED, www.msf-dgf.ro at 1st of April 2009). Cost of associated treatment with methotrexate was added to that of tocilizumab, infliximab and rituximab.

Other medical costs are cost of hospitalizations of RA patients, calculated based on hospitalization rate for patients in each HAQ score category and the average cost per hospitalization day. Rates of hospitalization for patients in each HAQ score categories are those from NOAR study (Norfolk & Norwich university hospital, dept. of Rheumatology registry), where the HAQ score categories are: 0-0.5, 0.6-1.0, 1.1-1.5, 1.6-2.0, 2.1-2.5, 2.6-3.0.

The per diem cost for hospitalizations was calculated based on average DRG I12B (Infections/inflammations of bones and articulations, w procedures on the musculoskeletal system, w severe CC) reimbursement from the National Health Insurance House.

Administration cost of drugs was also considered due to the compulsory intra-hospital administration of biologic drugs, either as inpatient or as day-Hospital stay. Costs for DayH administration were calculated based on average number of dayH episodes per year estimated by the experts, and the cost per dayH stay.

Cost of drugs monitoring include average resource use (annual number of tests) and cost of diagnostic and laboratory services for each drug involved in the sequences of treatment. Average consumption is detailed in Table 3.

The Indirect cost is cost incurred with loss of productivity, loss and/or decrease of work capacity due to RA and HAQ severity. This cost was estimated based on indicators used for measuring loss and/or decrease of work capacity used, from Kobelt, 1999. Costs at local level are estimated by using average annual gross salary figure, from the National Institute for Statistics (Monthly Statistical Bulletin, 2008).

Results of evaluation of costs are presented in Table 3.

Table 2. Average consumption of monitoring services for treatment with infliximab, tocilizumab and rituximab

<table>
<thead>
<tr>
<th>Type of services</th>
<th>Frequency Infliximab</th>
<th>Frequency Tocilizumab</th>
<th>Frequency Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray - chest</td>
<td>3,3</td>
<td>1</td>
<td>2,4</td>
</tr>
<tr>
<td>X-ray- hand joints</td>
<td>1,6</td>
<td>2</td>
<td>1,3</td>
</tr>
<tr>
<td>ECG</td>
<td>2</td>
<td>1</td>
<td>1,0</td>
</tr>
<tr>
<td>Rheumatoid factor (rf)</td>
<td>1,5</td>
<td>4</td>
<td>1,0</td>
</tr>
<tr>
<td>Blood count</td>
<td>3,4</td>
<td>4</td>
<td>3,5</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR)</td>
<td>4,5</td>
<td>12</td>
<td>4,1</td>
</tr>
<tr>
<td>AspAT</td>
<td>2,8</td>
<td>4</td>
<td>3,0</td>
</tr>
<tr>
<td>AIAT</td>
<td>5,1</td>
<td>4</td>
<td>4,6</td>
</tr>
<tr>
<td>Creatinine</td>
<td>4,5</td>
<td>3</td>
<td>4,1</td>
</tr>
<tr>
<td>CRP</td>
<td>4,5</td>
<td>12</td>
<td>4,1</td>
</tr>
<tr>
<td>Urine tests</td>
<td>4,1</td>
<td>2</td>
<td>4,1</td>
</tr>
<tr>
<td>Antigene HBS</td>
<td>5,1</td>
<td>1</td>
<td>4,6</td>
</tr>
<tr>
<td>Anti-HCV antibodies</td>
<td>4,1</td>
<td>1</td>
<td>3,8</td>
</tr>
<tr>
<td>Immunoglobulin concentration</td>
<td>1,8</td>
<td>4</td>
<td>1,5</td>
</tr>
</tbody>
</table>

Source of data: Study on cost-effectiveness evaluation of the treatment using tocilizumab, Roche Romania
The resulting Incremental Cost-Effectiveness Ratio (ICER) is 58,866 Rol per QALY gained (CI: 37,428 – 80,303). This ratio compares favorably with other treatments reimbursed by the National Health Insurance House. Results were tested using one-way sensitivity analysis, by varying first the effectiveness of treatment sequence including tocilizumab with 10% decrease, and second, by varying the cost discount rate from 6% to 3.5%. The resulting ICERs were 65,406 Rol per QALY gained, and 73,008 Rol per QALY gained respectively.

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modeling tool was developed by THEMA Research Limited for F. Hoffman-La Roche.

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