Extended report

Pharmacoeconomic study of patients with chronic inflammatory joint disease before and during infliximab treatment

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Keywords: rheumatoid arthritis, cost, infliximab
Abbrevations: ACR, American College of Rheumatology; CI, confidence interval; CRP, C-reactive protein; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, inter quartile range; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; VAS, visual analogue scale
Objective: To evaluate medical and work disability costs for patients with chronic inflammatory joint disease during one year before and one year after institution of infliximab treatment in routine clinical practice.

Methods: Starting from 1999 we systematically recorded clinical and laboratory variables for patients treated with biologicals for inflammatory rheumatic diseases at Helsinki University Central Hospital. From this database we collected clinical information on 96 patients for whom infliximab was started during the period 1999 to 2001. Economic analyses were based on costs incurred due to outpatient and inpatient visits, orthopaedic operations, drugs used, and days on sickness or rehabilitation allowance. Medical and work disability costs were calculated separately for the one-year period before (period I) and one-year period after institution of infliximab (period II).

Results: Of the 96 patients, with arthritis duration of 16 (range 3-43) years, 74 completed the one-year infliximab treatment. Their clinical and laboratory variables improved significantly. The mean increase in medical costs during period II was €12 015 (95% CI: 6 496 to 18 076). A minimal decrease in work disability costs occurred: a mean decrease of €130 (95% CI: -1 268 to 1 072).

Conclusions: One year treatment with infliximab in patients with long-standing aggressive arthritis showed a good clinical effect but raised medical costs significantly and work disability costs failed to show substantial decrease. Starting infliximab in earlier stages of chronic arthritis could in long term prevent work disability and thus decrease the total costs to society.

Rheumatoid arthritis (RA) is a chronic debilitating disease that affects 0.5 to 1% of populations all over the world.[1] Its economic burden is substantial for both the patients and for society; work disability being its most expensive consequence.[2] In cross-sectional studies the percentages of work disability in RA patients varied from 13% after a mean disease duration of 6 months to 67% after a mean disease duration of 15 years.[3]

Lately, biological drugs with a quick clinical effect, have been available. They reduce disease symptoms significantly and even slow disease progression, but they are more costly than the traditional disease-modifying anti-rheumatic drugs (DMARDs).[4][5] Infliximab, etanercept, and adalimumab have also shown good clinical effect in other rheumatic diseases such as psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and adult-onset Still’s disease.[6][7][8]

In the ATTRACT study, 428 RA patients received infliximab and methotrexate or methotrexate alone for one year.[5] The effect of infliximab on disease progression and related costs and utilities was estimated with the Markov model based on epidemiological studies in Sweden and the United Kingdom. Treatment with infliximab for one year saved €6 853 in Sweden and €1 897 in the UK in total costs, partly offsetting treatment cost. Cost per quality-adjusted life-year (QALY) gained was €3 440 in Sweden and €34 800 in the UK for one year of treatment, sums within the range considered acceptable.[9] Another study, using the results of the ATTRACT trial and the Markov computer simulation model, calculated for infliximab a marginal cost-effectiveness ratio of US $9 100 per discounted QALY gained, also cost-effective.[10] A Dutch study, modeling the 5-year cost effectiveness of different treatment strategies including traditional DMARDs, leflunomide and etanercept in RA patients, showed that the best effect on disease activity and QALY could be achieved with treatment including etanercept. The greater effectiveness resulted in reduced medical and nonmedical costs compared with traditional DMARDs by 16% and 33% respectively, omitting the costs of medication.[11]
The effect of biologicals in controlling disease activity and even retarding radiological progression of RA compared to traditional DMARDs has been shown in randomised controlled trials. The price of these drugs, however, sets a limit on their use, so it is important to compare the effects and total costs of traditional DMARDs with those of biologicals also in routine clinical practice.

Finland has national recommendations for prescribing biological therapy for RA: treatment with a combination of DMARDs including methotrexate and low dose of corticosteroids should have failed, and the patient should have active disease: >6 swollen joints, >6 tender joints, >45 min of morning stiffness, and an erythrocyte sedimentation rate (ESR) >30 mm/h or C-reactive protein (CRP) > 28 mg/l or both, and the American Rheumatism Association (ARA) functional class I to III (www.kaypahoito.fi/nivelreuma; Finnish current care guidelines for the management of rheumatoid arthritis). For other patients with chronic arthritis there are no official national recommendations in the use of biologicals. In clinical practice, the above mentioned criteria have been modified and non-RA patients are considered eligible to receive biologicals if they have chronic peripheral arthritis that fails to respond to a combination of DMARDs including methotrexate and low dose of corticosteroids and ESR >30 mm/h or CRP > 28 mg/l or both. If a patient fails to achieve 50% of the American College of Rheumatology (ACR) response criteria in 3 months or loses the response later, treatment is discontinued.[12] Biologicals are contraindicated in the case of chronic infections.

The cost-effectiveness of biologicals has been explored mostly with models based on results of large, randomised, controlled clinical trials. Results depend very much on methods and on unit costs and on the reimbursement system in each country.

We wanted to explore the medical and work disability costs of arthritis patients receiving infliximab treatment in routine clinical practice in a single rheumatological centre during one year and to compare these costs to those incurred during the year before infliximab.

Patients and methods
Between 1999 and 2001 at Helsinki University Central Hospital, infliximab was started in 118 patients with arthritis and we selected for the study 96 patients with medical records available at least during the preceding year. The 22 excluded patients had similar disease characteristics as the 96 included patients. Of the 96 patients: 63 (66%) were female; mean age was 48 (range 23-76) years and mean disease duration 16 (range 3-43) years. Besides 65 patients with RA, 8 patients had chronic reactive arthritis, 8 juvenile idiopathic arthritis, 6 psoriatic arthritis, 6 ankylosing spondylitis, 2 adult-onset Still’s disease, and one SAPHO syndrome. Mean disease duration in RA patients was 14 (range 2-41) and in non-RA patients 18 (range 3-43) years. All the non-RA patients had active peripheral arthritis (polyarthritis in 23 and mono- or oligoarthritis in 8 cases).

All patients were using DMARDs, 61% as monotherapy and 39% in various combinations. Methotrexate was the most common DMARD either as monotherapy or in combinations (table 1).

Table 1. Use of DMARDs and corticosteroids at the start of infliximab therapy.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>63 (66%)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>16 (17%)</td>
</tr>
</tbody>
</table>
Cyclosporin-A 15 (16%)
Leflunomide 14 (15%)
Podophyllotoxin 12 (13%)
Azathioprine 12 (13%)
Sulfasalazine 11 (11%)
Gold salts, i.m. or p.o. 10 (10%)
D-penicillamine 1 (1%)
Corticosteroids 79 (82%)

Strategy:
No drugs 0
Single therapy 13 (14%)
Single therapy with corticosteroids 45 (47%)
Corticosteroids alone 0
Combination therapy 4 (4%)
Combination therapy with corticosteroids 34 (35%)

Data were collected each time the patient visited the rheumatology unit. At the first visit we recorded information on age, diagnosis, disease duration, current treatment with DMARDs and corticosteroids, number of swollen (of 66) and tender (of 68) joints, patient’s global assessment of disease activity (visual analogue scale = VAS) and patient’s assessment of pain (VAS), and physician’s global assessment of disease activity (VAS), and ESR, CRP, and physical function by the Finnish Health Assessment Questionnaire (HAQ).[13] At every visit we registered adverse events and changes in treatment.

Infliximab was started with a dosage of 3 mg/kg, which was rounded off to the nearest 100 mg and was administered at weeks 0, 2, 6 and every 8 weeks thereafter. The dose or the interval could be adjusted if the response was insufficient.

The study was performed according to the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Helsinki University Central Hospital.

Economic data
Economic data were collected from case records for the one year before start of infliximab treatment (period I) and for the following one year (period II) including also data of patients discontinuing infliximab prior to one year.

Medical costs
We collected data on number of visits in the outpatient clinic and in the day unit, on inpatient stays in the rheumatology ward or in other wards, and on number of orthopaedic operations. We also gathered data on doses (mg) of DMARDs and corticosteroids and on duration (days) of treatment. We did not include non-steroidal anti-inflammatory drugs (NSAIDs) and other painkillers and drugs for nonrheumatic diseases because use of these drugs was not fixed and specified on every visit.
Because costs for aid appliances, transportation, rehabilitation, and assistive devices were excluded, we use the term “medical costs” instead of “direct costs”, referring to the most relevant medical costs.

**Work disability costs**
We recorded patient’s occupation, employment status, and number of days off work from case records, which included duplicate copies of certificates issued by a doctor documenting the patient’s work incapacity for claiming for sickness or rehabilitation allowance or disability pension. Rehabilitation allowance is a cash benefit for persons who go through medical or surgical interventions or take part in a rehabilitation programme to restore work ability and thus have to be absent from their regular work for at least one year. Information on median wages by occupation in 2002 came from the Official Statistics Finland. Because wages increased approximately 3% per year, we calculated the income of the year for which patient data were collected. The supplementary social welfare expenses (32.2% of income) were added to yield the monetary value of work productivity. The cost of lost productivity was calculated per day.

In 39 patients, who had retired before study entry, we included only medical costs to the analyses because the disability costs remained unchanged during the study period. Number of sickness absence days was calculated for each full-or half-time working patient and multiplied by earnings per day. We use the term “work disability costs” instead of “indirect costs” because not all indirect costs were calculated.

**Unit costs**
Unit costs of outpatient and day-unit visits came from the Helsinki University Central Hospital Catalogue for 2002 and the total costs of hospitalisations (including laboratory and radiological examinations, operations and drugs) of every patient were obtained from the financial department of Helsinki University Central Hospital or from local hospitals. The Finnish Pharmacotherapy Catalogue 2002 provided drug prices. The price of infliximab is included in the cost of a day-unit visit for a patient receiving infliximab or in the cost of a visit to rheumatology ward in Helsinki. In Euros, the 2002 price of infliximab per 100 mg was €538.37. The cost of outpatient visit was €106. The usual cost of day unit visit was €436 and for an infliximab patient €1 430.

In Helsinki University Central Hospital, infliximab infusions are given in the day-unit or in the rheumatology ward. At entry, the first 105 infliximab infusions (15%) were given in the rheumatology ward, but the last 592 infusions (85%) in the day-unit. The costs of tests and investigations are included in the price of a visit in the outpatient clinic.

Statistical analyses
Results are expressed as mean or median, standard deviation (SD) or range, and 95% confidence intervals (CI). As the cost data were skewed, confidence intervals for the means were obtained by bias-corrected bootstrapping (10 000 replications).[14] Analysis of clinical outcomes was performed according to the last-observation carried-forward method. Statistical comparison of changes in outcome measurements was performed by the Wilcoxon signed ranks test (Monte Carlo p-value) and Hodges-Lehmann estimation of median difference.

**Results**
Of the 96 patients, 22 (23%) discontinued infliximab prior to one year (14 patients with failure to respond by >ACR 50%, 3 with allergic reactions, one with lupus-like dermatitis, one with cerebral
haemorrhage, one with increasing proteinuria due to kidney amyloidosis, one for remission, one for personal problems). The discontinuations occurred evenly throughout the treatment period (figure). The discontinuation rate (16%) in the group of non-RA patients was lower than in RA patients (26%).

Table 2. Change in clinical variables during the second study year (period II) in all patients (N=96).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline Median (IQR)</th>
<th>Change to months 12 Median (95% CI) †</th>
</tr>
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<tbody>
<tr>
<td>Number of swollen joints</td>
<td>13 (7, 20)</td>
<td>-9 (-11 to -7)</td>
</tr>
<tr>
<td>Number of tender joints</td>
<td>18 (10, 25)</td>
<td>-12 (-15 to -10)</td>
</tr>
<tr>
<td>Pain (VAS)</td>
<td>7 (5, 8)</td>
<td>-3 (-4 to -2)</td>
</tr>
<tr>
<td>Patients global assessment (VAS)</td>
<td>7 (6, 8)</td>
<td>-4 (-5 to -3)</td>
</tr>
<tr>
<td>Physicians global assessment (VAS)</td>
<td>7 (5, 8)</td>
<td>-4 (-5 to -3)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.37 (1.00, 2.12)</td>
<td>-0.56 (-0.81 to -0.25)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>51 (31, 76)</td>
<td>-24 (-32 to -16)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>49 (22, 76)</td>
<td>-29 (-41 to -18)</td>
</tr>
</tbody>
</table>

† Hodges-Lehmann estimates of median difference.

By analysis based on intention to treat with last-observation carried-forward method all comparisons were at p<0.001.

When the patients were analysed as a whole group, a statistically significant improvement occurred in all clinical variables during one-year infliximab treatment compared to baseline (table 2). During infliximab therapy, 8 patients developed serious adverse events that led to hospitalisation: pneumonia in 5 patients and in one each: septic arthritis, cerebral hemorrhage, and lupus-like dermatitis. After treatment for the adverse event, infliximab was restarted for 6 of the patients. The number of orthopaedic operations changed little during the 2 years: 21 during period I and 24 during period II.

At the start of infliximab infusions, 47 (49%) patients were working full-time and 4 (4%) half-time; 39 (41%) were retired because of work disability, and 6 (6%) were retired because of age over 63. During period II, 5 patients retired because of RA-related work disability, one reduced her work contribution and continued to work half-time. On the other hand, one patient already on disability retirement began working half-time.
Table 3. Medical costs per patient during one year prior to (period I) and one year after institution of infliximab (period II).

<table>
<thead>
<tr>
<th>Costs (€)</th>
<th>Period I</th>
<th>Period II</th>
<th>Change ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (95% CI †)</td>
<td>Mean (95% CI †)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>Costs of outpatient visits</td>
<td>470 (418 to 541)</td>
<td>35 (19 to 76)</td>
<td>-435 (-498 to 385)</td>
</tr>
<tr>
<td>Costs of hospitalisations in rheumatology ward</td>
<td>6 526 (4 094 to 10 756)</td>
<td>9 662 (6 384 to 14 449)</td>
<td>§ 3 136 (1 575 to 7508)</td>
</tr>
<tr>
<td>Costs of day-ward visits</td>
<td>327 (222 to 500)</td>
<td>9 547 (8 786 to 10 317)</td>
<td>§ 9 220 (8 482 to 9 976)</td>
</tr>
<tr>
<td>Cost of drugs (DMARDs and corticosteroids)</td>
<td>1 861 (1 592 to 2 166)</td>
<td>952 (755 to 1 227)</td>
<td>-903 (-1 167 to -672)</td>
</tr>
<tr>
<td>Costs of hospitalisations in other wards</td>
<td>199 (26 to 970)</td>
<td>662 (205 to 1 923)</td>
<td>463 (-105 to 1 530)</td>
</tr>
<tr>
<td>Costs of orthopaedic operations</td>
<td>3 536 (1 988 to 5 760)</td>
<td>4 070 (1 656 to 6 484)</td>
<td>534 (-2 132 to 4 058)</td>
</tr>
<tr>
<td>Total costs</td>
<td>12 920 (10 031 to 17 416)</td>
<td>24 935 (20 699 to 31 874)</td>
<td>§ 12 015 (6 496 to 18 076)</td>
</tr>
</tbody>
</table>

† Confidence interval obtained by bias-corrected and accelerated bootstrapping (10 000 replications)
‡ Change in costs from period I to period II.
§ Including infliximab cost
Costs
A patient’s total annual medical cost increased on average €12 015 (95% CI: 6 496 to 18 076) during period II above the cost of period I. This increase in costs was mainly due to the increased number of visits to the day ward and hospitalisations in the rheumatology department for infliximab infusions.

The mean dose of infliximab infused per patient during period II was 1 687 mg, and the mean cost of a one-year treatment with infliximab was 9 080 €. Thus, the price of infliximab accounted for 75% of the increase in medical costs.

During period II, slight decrease incurred in the costs of outpatient visits, conventional DMARDs and corticosteroids.(table 3).

In period I the total number of hospitalisations was 65 (395 days) with a mean duration of 6 days, in period II the number of hospitalisations not related to infliximab administration was 47 (321 days) with a mean duration of 7 days. The reasons of hospitalisation in period I were: 63% for active joint disease; 19% for joint injections; 9% for infections; 9% for other reasons. In period II, excluding visits for infliximab administration: 57% for active joint disease; 17% for infections; 15% for joint injections; 11% for other reasons. The 22 patients who discontinued infliximab prior to one year were responsible for 58% of hospitalisation costs not related to infliximab administration in period II.

We also calculated separately the mean cost of the rheumatology ward visits for infusing infliximab: €5 090 (95% CI: 3 152 to 7 029) and the day-ward visits for infusing infliximab: €9 052 (95% CI: 7 950 to 9 447). Excluding the costs due to infliximab, mean rheumatology ward cost increased during period II: mean rheumatology ward costs during period I were €2 332 (95% CI: 1 720 to 3 211), compared with the costs of €4 751 (95% CI: 1 539 to 7 602) during period II. Calculated analogically, the costs of day-ward visits during period I were €327 (95% CI: 222 to 500), and during period II were €495 (95% CI: 359 to 722).

Mean work disability costs for those 51 patients available for the active work force at baseline were €7 166 (95% CI: 4 327 to 12 047) during period I. During period II the costs slightly decreased, the mean change being -130 (95% CI : -1 268 to 1 072). During period I, 11 patients, and during period II, 12 patients were on rehabilitation allowance. The mean number of days off work on short-term sick-leave or rehabilitation allowance during period I was 121, and increased during period II to 141.

Discussion
In our analysis of data for 96 arthritis patients treated with infliximab the improvement in clinical variables in period II was significant for the whole group. However, 14 patients failed to respond to infliximab.

Medical costs increased significantly during treatment with infliximab when compared to the earlier low medical costs. The main reason for this increase is the price of infliximab itself. At our institution, for drug safety reasons the very first infusions of infliximab were given in the rheumatology ward, and this increase in medical costs can cause a bias in comparison with other studies.
Cost of hospitalisation in the rheumatology ward for reasons other than infliximab infusions increased from a mean of €2 332 to €4 751 and the most frequent reason of hospitalisation in period II was the worsening of arthritis after discontinuation of infliximab. The increase in infection rates did not considerably affect the hospitalisation costs.

Visits to outpatient clinic decreased significantly because patients were examined by a physician every time before infliximab infusion. The good response to treatment is also reflected in the decreased costs of DMARDs and corticosteroids during treatment with infliximab. The cost of orthopaedic operations remained at the same level as a year before.

Although before infliximab all 96 patients had been treated for several years with more than one traditional DMARD, 39 (41%) were work-disabled because of RA, with 51 (53%) patients available for the active work force. Taking into account that the mean duration of the disease was 16 years, and these were the patients with the most active arthritis at the time, the number of patients still working is, however, very high.

Work-disability costs for those 51 patients remained at the same level during periods I and II. Number of days off work during treatment with infliximab even increased. This can be explained with the longstanding active arthritis that had damaged their joints to such an extent that the patients could not regain work ability despite suppression of disease activity. Another reason is that patients on long-term sickness allowance are already adapted to not working, and a return to the active workforce is demanding.

Infliximab was the first biological available in Finland, starting from 1999, and our patients were the very first patients with the most active arthritis receiving biological treatment at Helsinki University Central Hospital. This group was very heterogeneous, having other arthritis diagnoses besides RA that can result in bias in comparisons with other series. Between 1999 and 2001 besides infliximab, etanercept was started in two and anakinra in one patient.

The first study of costs of RA patients treated with biologicals (etanercept and infliximab) in clinical practice was done in Sweden.[15] Without taking into account the cost of biologicals, the direct costs were reduced by 40% during the first treatment year, and indirect costs remained unchanged. Total costs increased in one year by €12 183 (44%) from a mean of €27 447 to €39 630. Despite differences among studies, this increase in total costs is comparable with our findings. As the majority of patients in the Swedish study were treated with etanercept, the medical costs for administering the drug were lower. The other reason for lower medical costs on the second study year can be that patients who discontinued treatment prior to one year were excluded from the Swedish analyses. The number of excluded patients was 44 (28% of the whole group); 10 (6%) discontinued due to treatment failure. In our study, the number of patients discontinuing treatment because of treatment failure was higher 14 (15%), and they are included in our analyses.

We can thus conclude that although our patients with longstanding active arthritis had a very good clinical effect with infliximab infusions, the medical costs increased significantly, and treatment did not change their work status during one year. Starting infliximab or any other biological treatment in an earlier phase of arthritis when a patient is still able to work could result in decreased work disability costs. Further investigations are needed to assess the long-term effect of biologicals in the treatment of RA and other inflammatory arthritis in routine clinical practice with a special emphasis upon work ability and costs for society.
Acknowledgements
This study was supported by The National Graduate School for Musculoskeletal Diseases and by grants from the Helsinki University Central Hospital Research Funds and from the Finska Läkaresällskapet. We thank Mrs. Arja Kaarto for practical work with the database.

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Competing interests: None declared

Figure. Discontinuations of treatment during 54 weeks of infliximab.

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Ann Rheum Dis published online December 8, 2005

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