

EXTENDED REPORT

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

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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, clinical and laboratory variables for patients treated with biological agents for inflammatory rheumatic diseases were systematically recorded at Helsinki University Central Hospital. From this database clinical information was collected on 96 patients in whom infliximab was started during the period 1999 to 2001. Economic analyses were based on costs incurred because of 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 the one year period after institution of infliximab (period II).

Results: Of the study group of 96 patients (arthritis duration 16 years (range 3 to 43)), 74 completed one year of infliximab treatment. Their clinical and laboratory variables improved significantly. The mean increase in medical costs during period II was €12 015 (95% confidence interval, 6496 to 18 076). A minimal decrease in work disability costs occurred—mean decrease €130 (–1268 to 1072).

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

Rheumatoid arthritis is a chronic debilitating disease that affects 0.5–1% of populations all over the world.¹ Its economic burden is substantial both for the patients and for society, work disability being its most expensive consequence.² In cross sectional studies the percentage of work disability in patients with rheumatoid arthritis varied from 13% after a mean disease duration of six months to 67% after a mean disease duration of 15 years.³

Lately, biological drugs with a quick clinical effect have become available. They reduce disease symptoms significantly and even slow disease progression, but they are more costly than the traditional disease modifying antirheumatic 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.^{6–8}

In the ATTRACT study, 428 rheumatoid arthritis 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 €6853 in Sweden and €1897 in the UK in total costs, partly offsetting treatment cost. Cost per quality adjusted life year (QALY) gained was €3440 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 \$9100 per discounted QALY gained, also cost-effective.¹⁰ A Dutch study, modelling the five year cost-effectiveness of different treatment strategies including traditional DMARDs, leflunomide and etanercept, in rheumatoid arthritis patients, showed

that the best effect on disease activity and QALY could be achieved with treatment that included etanercept. The greater effectiveness resulted in reduced medical and non-medical costs compared with traditional DMARDs, by 16% and 33%, respectively, omitting the costs of the drugs.¹¹

The effect of biological agents in controlling disease activity and even retarding radiological progression of rheumatoid arthritis compared with 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 biological agents in routine clinical practice as well.

Finland has national recommendations for prescribing biological agents for rheumatoid arthritis: treatment with a combination of DMARDs including methotrexate and low dose of corticosteroids should have failed, and the patient should have active disease, as indicated by the following: more than six swollen joints; more than six tender joints; more than 45 minutes of morning stiffness; an erythrocyte sedimentation rate (ESR) of >30 mm/h or a C reactive protein of >28 mg/l, or both; and 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

Abbreviations: ACR, American College of Rheumatology; ATTRACT, Anti-Tumor necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy; DMARD, disease modifying antirheumatic drug; HAQ, health assessment questionnaire; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; QALY, quality adjusted life year; VAS, visual analogue scale

Table 1 Use of DMARDs and corticosteroids at the start of infliximab treatment

Therapy	Number (%)
Drugs	
Methotrexate	63 (66%)
Hydroxychloroquine	16 (17%)
Ciclosporine-A	15 (16%)
Leflunomide	14 (15%)
Podophyllotoxin	12 (13%)
Azathioprine	12 (13%)
Sulfasalazine	11 (11%)
Gold salts, im or po	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%)

im, intramuscular; po, oral.

recommendations for the use of biological agents. In clinical practice, the above mentioned criteria have been modified, and non-rheumatoid patients are considered eligible to receive biological agents if they have chronic peripheral arthritis that fails to respond to a combination of DMARDs, including methotrexate and low dose of corticosteroids, and have an ESR of >30 mm/h or a C reactive protein of >28 mg/l or both. If a patient fails to achieve 50% of the ACR response criteria in three months, or loses the response later, treatment is discontinued.¹² Biological agents are contraindicated in cases of chronic infection.

The cost-effectiveness of biological agents has been explored mostly with models based on the 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.

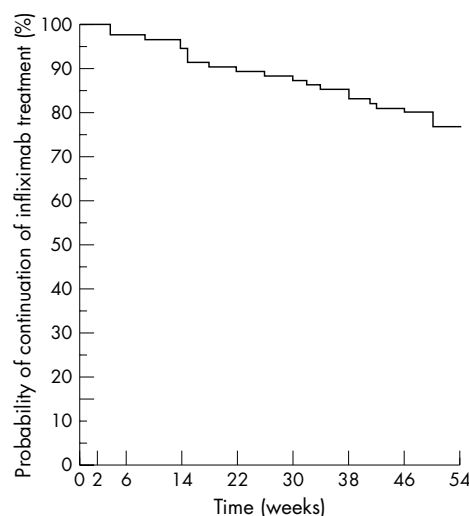
We wanted to explore the medical and work disability costs of arthritis patients receiving infliximab treatment in routine clinical practice in a single rheumatological centre during one year, and to compare these costs with those incurred during the year before infliximab was first used.

METHODS

Between 1999 and 2001 at Helsinki University Central Hospital, infliximab was started in 118 patients with arthritis. We selected for the study 96 patients with medical records available at least during the preceding year. The 22 patients excluded had similar disease characteristics to the 96 included patients. Of the 96 patients, 63 (66%) were female, mean age was 48 years (range 23 to 76), and mean disease duration was 16 years (range 3 to 43). Sixty five of the patients had rheumatoid arthritis, eight had chronic reactive arthritis, eight juvenile idiopathic arthritis, six had psoriatic arthritis, six had ankylosing spondylitis, two had adult onset Still's disease, and one had SAPHO syndrome. Mean disease duration in the rheumatoid arthritis group was 14 years (range 2 to 41) and in the non-rheumatoid group, 18 years (range 3 to 43). All the non-rheumatoid patients had active peripheral arthritis (polyarthritis in 23 and mono- or oligoarthritis in eight).

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).

Data were collected each time the patient visited the rheumatology unit. At the first visit we recorded information

**Figure 1** Discontinuations of treatment during 54 weeks of infliximab.

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)), patient's assessment of pain (VAS), physician's global assessment of disease activity (VAS), ESR, C reactive protein, and physical function by the Finnish Health Assessment Questionnaire (HAQ).¹³ At each visit we recorded adverse events and changes in treatment.

Infliximab was started at a dosage of 3 mg/kg, which was rounded off to the nearest 100 mg and was given in 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 undertaken in accordance with 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 year (period II), including data on patients discontinuing infliximab before the end of period II.

Medical costs

We collected data on the number of visits to the outpatient clinic and to the day unit, on inpatient stays in the rheumatology ward or in other wards, and on the number of orthopaedic operations. We also gathered data on dosage (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 non-rheumatic diseases because the 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 patients' 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

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

Variable	Baseline median (IQR)	Change to month 12* (median (95% CI))
Number of swollen joints	13 (7 to 20)	-9 (-11 to -7)
Number of tender joints	18 (10 to 25)	-12 (-15 to -10)
Pain (VAS)	7 (5 to 8)	-3 (-4 to -2)
Patient's global assessment (VAS)	7 (6 to 8)	-4 (-5 to -3)
Physician's global assessment (VAS)	7 (5 to 8)	-4 (-5 to -3)
HAQ	1.37 (1.00 to 2.12)	-0.56 (-0.81 to -0.25)
ESR (mm/h)	51 (31 to 76)	-24 (-32 to -16)
C reactive protein (mg/l)	49 (22 to 76)	-29 (-41 to -18)

*Hodges-Lehmann estimates of median difference.

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

CI, confidence interval; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IQR, interquartile range; VAS, visual analogue scale.

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 wage by occupation in 2002 came from the Official Statistics Finland. Because wages increased by 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 for the analyses because the disability costs remained unchanged during the study period. The 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 hospital admissions (including laboratory and radiological examinations, operations, and drugs) for 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 an outpatient visit was €106. The usual cost of a day unit visit was €436 and for an infliximab patient €1430.

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 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 carried out using the last observation carried forward method. Statistical comparison of changes in outcome measurements was done using the Wilcoxon signed ranks test (Monte Carlo p value) and the Hodges-Lehmann estimation of median difference.

RESULTS

Of the 96 patients, 22 (23%) discontinued infliximab before one year (14 patients because of failure to respond by >ACR 50%, three with allergic reactions, one with lupus-like dermatitis, one with cerebral haemorrhage, one with increasing proteinuria because of renal amyloidosis, one for remission, one for personal problems). The discontinuations occurred evenly throughout the treatment period (fig 1).

The discontinuation rate (16%) in the non-rheumatoid group patients was lower than in rheumatoid arthritis group (26%).

When the patients were analysed as a whole group, a significant improvement occurred in all clinical variables during one year of infliximab treatment compared with baseline (table 2).

During infliximab treatment, eight patients developed serious adverse events that led to hospital admission: pneumonia in five patients and in one each: septic arthritis,

Table 3 Medical costs per patient during one year before (period I) and one year after the institution of infliximab (period II)

Costs (€)	Period I (mean (95% CI*))	Period II (mean (95% CI*))	Change† (mean (95% CI))
Costs of outpatient visits	470 (418 to 541)	35 (19 to 76)	-435 (-498 to 385)
Costs of hospital admissions to rheumatology ward	6526 (4094 to 10 756)	9662 (6384 to 14 449) ‡	3136 (1575 to 7508)
Costs of day ward visits	327 (222 to 500)	9547 (8786 to 10 317) ‡	9220 (8482 to 9976)
Cost of drugs (DMARDs and corticosteroids)	1861 (1592 to 2166)	952 (755 to 1227)	-903 (-1167 to -672)
Costs of hospital admissions to other wards	199 (26 to 970)	662 (205 to 1923)	463 (-105 to 1530)
Costs of orthopaedic operations	3536 (1988 to 5760)	4070 (1656 to 6 484)	534 (-2132 to 4058)
Total costs	12 920 (10 031 to 17 416)	24 935 (20 699 to 31 874) ‡	12 015 (6496 to 18 076)

*Confidence interval obtained by bias corrected and accelerated bootstrapping (10 000 replications).

†Change in costs from period I to period II.

‡Including infliximab cost.

CI, confidence interval; DMARD, disease modifying antirheumatic drug.

cerebral haemorrhage, and lupus-like dermatitis. After treatment for the adverse event, infliximab was restarted in six of these patients. The number of orthopaedic operations changed little during the two years: 21 during period I and 24 during period II.

At the start of infliximab infusions, 47 patients (49%) were working full time and four (4%) half time; 39 (41%) were retired because of work disability, and six (6%) were retired because their age was over 63. During period II, five patients retired because of rheumatoid arthritis related work disability, while 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.

Costs

A patient's total annual medical cost increased on average by €12 015 (95% CI, 6496 to 18 076) during period II above the cost of period I. This increase in costs was mainly accounted for by the increased number of visits to the day ward and hospital admissions in the rheumatology department for the infliximab infusions.

The mean dose of infliximab infused per patient during period II was 1687 mg, and the mean cost of a one year treatment with infliximab was €9080. Thus the price of infliximab accounted for 75% of the increase in medical costs.

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

In period I the total number of hospital admissions was 65 (395 days), with a mean duration of six days; in period II the number of hospital admissions not related to infliximab administration was 47 (321 days), with a mean duration of seven days. The reasons for hospital admission 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 before one year were responsible for 58% of hospital admission costs not related to infliximab administration in period II.

We also calculated separately the mean cost of the rheumatology ward visits for infusing infliximab: €5090 (95% CI, 3152 to 7029), and the day ward visits for infusing infliximab: €9052 (7950 to 9447). Excluding the cost of infliximab, mean rheumatology ward cost increased during period II. Mean rheumatology ward costs during period I were €2332 (1720 to 3211), v €4751 (1539 to 7602) during period II. Calculated analogically, the costs of day ward visits during period I were €327 (222 to 500), and during period II they were €495 (359 to 722).

Mean work disability costs for those 51 patients available for the active work force at baseline were €7166 (4327 to 12 047) during period I. During period II the costs decreased slightly, the mean change being -130 (-1268 to 1072). During period I, 11 patients were on rehabilitation allowance, and during period II, 12 patients. The mean number of days off work on short term sick leave or rehabilitation allowance during period I was 121, and this 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.

Medical costs increased significantly during treatment with infliximab when compared with 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 could cause bias in comparison with other studies.

Cost of hospital admissions to the rheumatology ward for reasons other than infliximab infusions increased from a mean of €2332 to €4751, the most frequent reason for admission in period II being the worsening of arthritis after discontinuation of infliximab. An increase in infection rates did not have much effect on the hospital admission costs.

Visits to the outpatient clinic decreased significantly because patients were examined by a physician on each occasion before an infliximab infusion was given. 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 in the year before.

Although all 96 patients had been treated for several years with more than one traditional DMARD before they were given infliximab, 39 (41%) were work disabled because of rheumatoid arthritis, while only 51 (53%) were 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. The number of days off work during treatment with infliximab even increased. This can be explained by 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 agent available in Finland, starting from 1999, and our patients were the very first patients, and those with the most active arthritis, receiving biological treatment at Helsinki University Central Hospital. This group was heterogeneous, having other arthritis diagnoses besides rheumatoid arthritis, and this may result in bias in comparison with other series. A few patients were also treated with other biological agents: between 1999 and 2001, etanercept was started in two and anakinra in one.

The first study of costs of rheumatoid arthritis patients treated with biological agents (etanercept and infliximab) in clinical practice was undertaken in Sweden.¹⁵ Without taking into account the cost of these drugs, 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 of administering the drug were lower. Another reason for lower medical costs in the second study year might be that patients who discontinued treatment before completing the year were excluded from the Swedish analyses. Forty four patients were excluded in all (28% of the total cohort); 10 (6%) stopped taking the drug because of treatment failure. In our study, a larger number of patients discontinued treatment because of treatment failure (14 patients (15%)), and these were included in our analyses.

We can thus conclude that although our patients with longstanding active arthritis had a very good clinical response to infliximab infusions, the medical costs increased significantly, and treatment did not change their work status during the course of a 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 biological agents in the treatment of rheumatoid arthritis and other forms of inflammatory arthritis in routine clinical practice, with a special emphasis upon work ability and costs for society.

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