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Health-Related Quality of Life, Costs and Treatment of Inflammatory Rheumatic Diseases in Routine Practice

With special emphasis on biological drugs

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ACADEMIC DISSERTATION

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To my family

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals I-IV. The original publications are reprinted with the permission of the copyright holders. In addition, some unpublished results are presented.

I **Laas K**, Roine R, Räsänen P, Sintonen H, Leirisalo-Repo M; HUS QoL Study Group (2009b): Health-related quality of life in patients with common rheumatic diseases referred to a university clinic. Rheumatol Int 29:267–73.

II **Laas K**, Peltomaa R, Puolakka K, Kautiainen H, Leirisalo-Repo M (2009a): Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice. Clin Exp Rheumatol (Accepted 26.09.2008).

III **Laas K**, Peltomaa R, Puolakka K, Kautiainen H, Leirisalo-Repo M (2006): Pharmacoeconomic study of patients with chronic inflammatory joint disease before and during infliximab treatment. Ann Rheum Dis 65:924-8.

IV **Laas K**, Peltomaa R, Kautiainen H, Leirisalo-Repo M (2008): Clinical impact of switching from infliximab to etanercept in patients with rheumatoid arthritis. Clin Rheumatol 27:927-32.

ABBREVIATIONS

ACR	American College of Rheumatology
ANA	Antinuclear antibody
ARA	American Rheumatism Association
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
BASDAI	BATH ankylosing spondylitis disease activity index
CI	Confidence interval
CRP	C-reactive protein
DAS28	Disease activity score with 28 joints examined
DMARD	Disease-Modifying Anti-Rheumatic Drug
EULAR	European League Against Rheumatism
ESR	Erythrocyte sedimentation rate
FM	Fibromyalgia
HAQ	Stanford Health Assessment Questionnaire
HLA	Human leucocyte antigen
HRQoL	Health-related quality of life
ILAR	International League of Associations for Rheumatology
IQR	Interquartile range
JIA	Juvenile idiopathic arthritis
MCID	Minimally clinically important difference
MCP	Metacarpophalangeal joint
MID	Minimally important difference
MTX	Methotrexate
NSAID	Nonsteroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PIP	Proximal interphalangeal joint
PSA	Psoriatic arthritis
QALY	Quality-adjusted life year
QoL	Quality of life
RA	Rheumatoid arthritis
RAND-36	The RAND 36-Item Health Survey 1.0
RaQoL	Rheumatoid Arthritis Quality of Life (questionnaire)

RCT	Randomized control trial
ReA	Reactive arthritis
RF	Rheumatoid factor
RTX	Rituximab
SD	Standard deviation
SF-36	The Medical Outcomes Study Short Form 36 item Health Status Survey Questionnaire
SPA	Spondyloarthropathy
TNF	Tumour necrosis factor
VAS	Visual analogue scale

ABSTRACT

Rheumatoid arthritis (RA) and other chronic inflammatory joint diseases already begin to affect patients' health-related quality of life (HRQoL) in the earliest phases of these diseases. In treatment of inflammatory joint diseases, the last two decades have seen new strategies and treatment options introduced. Treatment is started at an earlier phase; combinations of disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids are used; and in refractory cases new drugs such as tumour necrosis factor (TNF) inhibitors or other biologicals can be started.

In patients with new referrals to the Department of Rheumatology of the Helsinki University Central Hospital, we evaluated the 15D and the Stanford Health Assessment Questionnaire (HAQ) results at baseline and approximately 8 months after their first visit. Altogether the analysis included 295 patients with various rheumatic diseases. The mean baseline 15D score (0.822, SD 0.114) was significantly lower than for the age-matched general population (0.903, SD 0.098). Patients with osteoarthritis (OA) and spondyloarthropathies (SPA) reported the poorest HRQoL. In patients with RA and reactive arthritis (ReA) the HRQoL improved in a statistically significant manner during the 8-month follow-up. In addition, a clinically important change appeared in patients with systemic rheumatic diseases. HAQ score improved significantly in patients with RA, arthralgia and fibromyalgia, and ReA.

In a study of 97 RA patients treated either with etanercept or adalimumab, we assessed their HRQoL with the RAND 36-Item Health Survey 1.0 (RAND-36) questionnaire. We also analysed changes in clinical parameters and the HAQ. With etanercept and adalimumab, the values of all domains in the RAND-36 questionnaire increased during the first 3 months. The efficacy of each in improving HRQoL was statistically significant, and the drug effects were comparable. Compared to Finnish age- and sex-matched general population values, the HRQoL of the RA patients was significantly lower at baseline and, despite the improvement, remained lower also at follow-up. Our RA patients

had long-standing and severe disease that can explain the low HRQoL also at follow-up.

In a pharmacoeconomic study of patients treated with infliximab we evaluated medical and work disability costs for patients with chronic inflammatory joint disease during one year before and one year after institution of infliximab treatment. Clinical and economic data for 96 patients with different arthritis diagnoses showed, in all patients, significantly improved clinical and laboratory variables. However, the medical costs increased significantly during the second period by €12 015 (95% confidence interval, 6 496 to 18 076). Only a minimal decrease in work disability costs occurred – mean decrease €130 (-1 268 to 1 072).

In a study involving a switch from infliximab to etanercept, we investigated the clinical outcome in 49 patients with RA. Reasons for switching were in 42% failure to respond by American College of Rheumatology (ACR) 50% criteria; in 12% adverse event; and in 46% non-medical reasons although the patients had responded to infliximab. The Disease Activity Score with 28 joints examined (DAS28) allowed us to measure patients' disease activity and compare outcome between groups based on the reason for switching. In the patients in whom infliximab was switched to etanercept for nonmedical reasons, etanercept continued to suppress disease activity effectively, and 1-year drug survival for etanercept was 77% (95% CI, 62 to 97). In patients in the infliximab failure and adverse event groups, DAS28 values improved significantly during etanercept therapy. However, the 1-year drug survival of etanercept was only 43% (95% CI, 26 to 70) and 50% (95% CI, 33 to 100), respectively.

Although the HRQoL of patients with inflammatory joint diseases is significantly lower than that of the general population, use of early and aggressive treatment strategies including TNF-inhibitors can improve patients' HRQoL effectively. Further research is needed in finding new treatment strategies for those patients who fail to respond or lose their response to TNF-inhibitors.

1. INTRODUCTION

Musculoskeletal disorders impose a considerable burden upon society because of long-term morbidity, disability, and costs. Among musculoskeletal diseases, rheumatoid arthritis (RA) leads to patients' incurring a significantly higher individual economic burden for society than does osteoarthritis (OA), for example, largely because of indirect costs (Maetzel et al. 2004). These indirect costs arise from sick-leaves, part-time work, and early retirement. The peak rate for work disability is at two years after symptom onset, ranging from 23% to 42% (Barrett et al. 2000). Several studies have shown that predictors of future productivity loss in early RA are a low education level, older age, severity of RA, and a disability score ≥ 1 measured by the Stanford Health Assessment Questionnaire (HAQ) (Puolakka et al. 2005).

Living with a chronic disease affects many aspects of an individual's life including health-related quality of life (HRQoL). In musculoskeletal diseases, the deterioration of HRQoL is often a result of long-term pain and reduced physical functioning. In a study of multiple musculoskeletal diseases, the worst HRQoL was in patients with OA, osteoporosis, RA, and fibromyalgia (Picavet and Hoeymans 2004). In patients with RA, the HRQoL is already affected in the early phases of the disease. Those with early RA report the greatest deterioration in bodily pain and in physical functioning, involving limitations in activities of daily living and work (West and Jonsson 2005).

The contemporary treatment strategies of RA aim to achieve remission or low disease activity and include early and aggressive treatment with disease-modifying anti-rheumatic drugs (DMARDs) as mono or combination treatment, and use of low-dose corticosteroids or biologicals or both in patients with severe disease unresponsive to conventional DMARDs. Randomized control trials (RCTs) have demonstrated the efficacy of tumour necrosis factor (TNF) inhibitors in reducing disease activity and slowing radiological progression (Moreland et al. 1997, Lipsky et al. 2000, Breedveld et al. 2006). In addition, recent studies have demonstrated the ability of TNF-inhibitors to improve RA patients' HRQoL (Han et al. 2007, Kimel et al. 2008, Mathias et al. 2000,

Mittendorf et al. 2007). The high costs of biologicals compared with conventional DMARDs, however, increase the costs of RA treatment substantially. Cost-effectiveness studies suggest that costs associated with use of TNF-inhibitors may be acceptable in relation to the benefits obtained (Russell 2008).

Although TNF-inhibitors have demonstrated good capability to suppress disease activity effectively, approximately one-third of patients still fail to respond (Lipsky et al. 2000, Weinblatt et al. 1999). Several studies have reported that switching from one TNF-inhibitor to another in the case of response failure can be a good alternative (Buch et al. 2007, Hyrich et al. 2007, Nikas et al. 2006).

The primary aim of our study was to follow patients with different rheumatic diseases during treatment with TNF-inhibitors and to evaluate their HRQoL, their costs, and in patients who were switched to the second TNF-inhibitor, also their clinical outcome. Another focus of our study was to assess the HRQoL of patients with different musculoskeletal disorders referred for the first time to Helsinki University Central Hospital and to evaluate any change in HRQoL after 8-month routine treatment.

2. REVIEW OF THE LITERATURE

2.1 Inflammatory joint diseases

2.1.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology that affects predominantly the synovial joints but can also induce extraarticular manifestations. RA has worldwide distribution with a prevalence estimated at 0.5 to 1% in studies across Europe, North America, Asia, and South Africa (Silman and Hochberg 2001). In Finland, the prevalence of clinically significant RA is 0.8% of the adult population. In 1995 the annual incidence was a reported 34 per 100 000 (Aho et al. 1998, Kaipiainen-Seppanen and Aho 2000). Women are affected two to three times more often than men, and RA incidence increases with age.

RA onset may be acute, subacute, or insidious, with the last course being the most common. The clinical course varies from a benign monocyclic to more frequent long-standing progressive disease that causes joint destruction even during the first years of the disease. RA commonly affects symmetrically the small peripheral joints of the hands and feet like the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints, but also the wrists, knees, cervical spine, glenohumeral joints, and hips.

RA is a systemic disease that may also affect other organs and tissues. The most common extraarticular manifestations include subcutaneous rheumatoid nodules, vasculitic skin lesions, secondary Sjögren syndrome, pericarditis, pleuritis, pulmonary interstitial fibrosis, mononeuritis multiplex, amyloidosis, and Felty's syndrome (Harris et al. 2005, Turesson et al. 2002).

The inflammation and destructive changes in joints lead to functional disability. This results in impaired social functioning, and in diminished work capacity or total work disability in patients of working age. The American

College of Rheumatology (ACR) has provided classification criteria for RA (Table 1) (Arnett et al. 1988).

Table 1. American College of Rheumatology classification criteria of rheumatoid arthritis. For the diagnosis of RA, a patient should have at least four of the seven criteria. Criteria 1-4 must have been present for at least 6 weeks.

1. Morning stiffness (1 hour or more)
2. Arthritis in three or more joint areas
3. Arthritis of the hand joints (PIP, MCP, wrist)
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes in a hand or wrist joint or both

PIP, proximal interphalangeal joint; MCP, metacarpophalangeal joint.

2.1.2 Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) begins before the age of 16 and is defined as a sterile inflammation of at least one joint lasting minimally for 6 weeks, and for which there is no defined diagnosis (Fink 1995). According to the classification proposed by the International League of Associations for Rheumatology (ILAR), JIA has seven clinical subtypes: oligoarthritis, seronegative polyarthritis, seropositive polyarthritis, systemic arthritis, enthesitis related arthritis, psoriatic arthritis, and undifferentiated arthritis (Petty et al. 2004).

JIA is the most common rheumatic disease in childhood. Prevalence estimates of JIA in children under age 16 published in the last 20 years in Scandinavian countries and in Estonia were 84 to 148 per 100 000 (Pruunsild et al. 2007, Gare and Fasth 1992, Moe and Rygg 1998). In other European

countries, the USA, and Canada, prevalence has ranged from 40 to 160 per 100 000 (Silman and Hochberg 2001).

Age of onset depends greatly on subtype. Among girls the incidence is highest between ages 1 and 3 years. Oligoarthritis is the most common subtype, comprising more than half of the JIA cases. The best long-term outcome has been associated with persistent oligoarthritis and the worst with rheumatoid factor (RF) -positive polyarthritis. Studies in the last 10 years have shown that only 40 to 60% of patients had inactive disease or were in clinical remission at follow-up. Despite the persistent disease activity in most patients with JIA, functional outcome has been reported as good at follow-up, with only 2 to 10% of patients suffering serious functional disability (Ravelli and Martini 2007).

2.1.3 Spondyloarthropathies

The spondyloarthropathies (SPAs) comprise five subtypes: ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PSA), enteropathic arthritis, and undifferentiated arthritis. AS is the most frequent subtype, being more prevalent than are undifferentiated arthritis and PSA, while enteropathic arthritis and ReA are even less prevalent. SPAs share similar features of disease, such as a typical pattern of peripheral arthritis affecting asymmetrically the lower limbs, absence of RF, and subcutaneous nodules typical to RA, a tendency toward radiographic sacroiilitis, familial aggregation, and association with human leucocyte antigen (HLA) B27.

2.1.3.1 Ankylosing spondylitis

AS is an HLA-B27-associated chronic inflammatory disease affecting the spine, sacroiliac joints, peripheral joints, and enthesis. AS predominantly appears in the second or third decade of life and its prevalence is 0.5% (Gran and Husby 1993). Clinically, AS is more common in males, with a male-to-

female ratio of 2:1 to 3:1. Most often the first clinical sign of AS is low back pain in the gluteal region, associated with a feeling of low back stiffness that is worse in the morning and can awaken the patient at night. The pain can radiate to the iliac crest, greater trochanteric region or down the dorsal thigh and is relieved by physical activity.

In the clinical picture, low back pain is often accompanied by chest pain, extra-articular tenderness, and arthritis of the hip, shoulder or knee joints. The common sites of extra-articular tenderness caused by enthesitis are the costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, or heels. Acute anterior uveitis or iridocyclitis can occur in 25 to 30% of AS patients at some time in the course of the disease.

The diagnosis of AS is based on clinical features. A definite diagnosis is usually established by radiographic evidence of bilateral sacroiliitis that is very seldom present in the early stages of disease. Therefore, presence of low back pain and positive family history for AS are critically important for diagnosis (Harris et al. 2005).

2.1.3.2 Reactive arthritis

ReA can be defined as a sterile synovitis that is preceded by 4 to 8 weeks by an infection usually in the gastrointestinal or genitourinary tract. The clinically diagnosed infection may involve diarrhea or nongonococcal urethritis. It can also be diagnosed by identifying the bacteria that most often cause ReA: *Chlamydia, Salmonella, Shigella, Yersinia, or Campylobacter.* In addition, other infectious agents such as *Clostridium, Mycoplasma, and Ureaplasma* have been suspected as triggering infections (Leirisalo-Repo 2005).

ReA is typically a disease of young adults, mean age 20 to 30 years. In ReA that occurs after a genitourinary infection, males are more affected. After a gastrointestinal infection, males and females are at similar risk for ReA. The

clinical pattern of ReA is asymmetrical arthritis in the lower limbs affecting one or several joints. Extraarticular manifestations can occur, such as urethritis, balanitis, conjunctivitis, iritis, entesopathy, low back pain, or skin syndromes such as keratodermia blenorrhagica or erythema nodosum. ReA diagnosis can be supported by laboratory tests that identify the arthritis-causing bacteria. When positive, they support a diagnosis of ReA but when negative, ReA cannot be ruled out.

2.2 Other rheumatic diseases

2.2.1 Osteoarthritis

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by erosions of the articular cartilage, marginal osteophytes, subchondral sclerosis, and biochemical and morphological changes in the synovium and joint capsule (Harris et al. 2005).

OA is the most frequent rheumatic disorder, and its occurrence is increasing with aging populations. Prevalence estimates of OA vary widely depending on the OA localisation and on diagnosis methodology. One of the largest OA prevalence surveys has been conducted in the USA – the Health Examination Survey and First National Health and Nutrition Examination Survey (Lawrence et al. 1998). Based on radiographic criteria, the prevalence of OA in the USA among adults aged 25 to 74 was 32.5 for the hands, 22.2 for the feet, and 3.8 per 100 for the knees. Prevalence increased similarly with age among men and women. In the age group 55 to 74, the corresponding prevalence ratios were 70% for the hands, 40% for the feet, 10% for the knees, and 3% for the hips (Silman and Hochberg 2001).

The most important symptom of OA is joint pain that can be typically use-related in the beginning of the disease, and in advanced OA can persist for several hours. Other OA symptoms are joint stiffness, tenderness, loss of movement, and joint instability. The diagnosis of OA is usually based on

interviews and clinical investigations. Radiographic investigations may be necessary to predict the evolution of the disease, to provide a baseline picture of the structural damage, and to indicate specific treatments. Laboratory tests are useless for diagnosing OA but can be helpful in excluding other diagnoses.

Management of OA includes pharmacological and nonpharmacological interventions, and in cases of severe joint destruction and pain, orthopaedic surgery. Nonpharmacological interventions mean patient education, weight-loss, exercise, orthoses, topical applications of heat or cold, use of canes and other interventions. Pharmacological interventions can be divided into symptomatic therapy and potentially disease-modifying therapy. Although acetaminophen (paracetamol) is the first choice of symptomatic therapy because of its safety and efficacy, the most commonly prescribed medications for OA patients are the nonsteroidal anti-inflammatory drugs (NSAIDs). Oral NSAIDs should be maintained at the lowest effective dose for the shortest duration (Zhang et al. 2007). The potentially disease-modifying therapies (for example, glucosamine, chondroitin sulphate, intraarticular hyaluronan) give a moderate clinically significant treatment benefit with low toxicity when compared to placebo, but no clinically important structure modification has been established (Towheed et al. 2005). Surgical interventions usually include osteotomy or joint replacement. Osteotomy can be effective in relieving pain and delaying the need for joint replacement. Joint replacement surgery is considered most frequently with OA of the hip or knee and should be considered in patients with radiographic evidence of OA, refractory pain, or disability (Jordan et al. 2003, Zhang et al. 2005).

2.2.2 Fibromyalgia

Fibromyalgia (FM) is a chronic pain syndrome affecting 0.5 to 2.0% of the general population (Silman and Hochberg 2001). In addition to pain, patients with FM complain about fatigue, sleep problems, stiffness, headaches, and psychological distress. FM is more prevalent in women: in a study from the

USA, 3.4% compared to 0.5% of men (Wolfe et al. 1995). For research purposes, the ACR has published classification criteria for FM that require the presence of widespread pain in combination with 11 or more tender points on examination of 18 anatomical sites. The diagnosis has to be made according to an interview and clinical examination because laboratory tests and radiographic examinations fail to show any abnormalities in patients with FM. The overall health status of these patients is poorer than that of the general population or patients with other conditions widely accepted as causing impairment (Hoffman and Dukes 2008).

Treatment of FM is focused on reducing pain, improving sleep, restoring physical functioning, maintaining social functioning, and improving emotional balance. According to European League Against Rheumatism (EULAR) recommendations, management of FM includes both pharmacological and nonpharmacological treatment. Effective nonpharmacological methods are heated pool treatment, individual exercise programs, and cognitive behavioural therapy. Pharmacological treatments include tramadol, paracetamol, and weak opioids for the management of pain. In addition, various anti-depressants can be used to reduce pain and improve function (Carville et al. 2008).

2.3 Assessment of HRQoL

2.3.1 General

Quality of life (QoL) is a broad-ranging concept that incorporates health states, as well as satisfaction with work, leisure time, level of independence, social relationships, and environment (Carr et al 1996). The World Health Organization (WHO) has defined QOL as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (Anonymous 1995). HRQoL is a multidimensional concept that encompasses an individual's physical, emotional, and social components associated with his/her medical condition or its treatment (Khanna and Tsevat 2007).

Interest in measuring HRQoL has increased markedly in recent decades. With advances in medical science and technology, an increasing number of people live contentedly with chronic diseases and disabilities. This change in the morbidity profile has evoked the need to evaluate the outcome of different treatments according to the patients' perspective.

HRQoL can be measured either with disease-specific or generic measurement tools. The generic instruments allow comparisons between patient groups with different diagnoses, whereas the disease-specific instruments give information about only one certain disease and its effect on health. Disease-specific instruments are, however, more sensitive to important health status differences essential for a particular disease. They are therefore successfully used for measuring results of specific treatments. A well-known example of a disease-specific instrument is the Rheumatoid Arthritis Quality of Life (RaQoL) questionnaire; this is the first patient-completed instrument specially designed for use with RA patients (de Jong et al. 1997). The RaQoL has proven able to distinguish better than generic instruments between different RA groups based on disease severity (Marra et al. 2005). The RaQoL questionnaire is easy to use, has a short administration time, and it deals with items and issues important for patients with RA (Russell 2008).

The generic instruments can be divided into profile and single index score measures. Profile measures describe the health state according to various physical and emotional dimensions such as physical functioning, bodily pain, general health, social functioning, and other dimensions. A well-known example of a generic instrument is the widely used Medical Outcomes Study Short Form 36 item Health Status Survey Questionnaire (SF-36). The single index score instruments produce a single value (utility score) on a 0-1 scale that provides an overall picture of the level of HRQoL and changes in it. Utility values are necessary for calculating the Quality-Adjusted Life Years (QALYs), developed to combine the quantity and quality of life into a single measure. The cost per QALY can be estimated and compared among different treatments in economic analyses. Utilities are derived from health status by assigning population-based weights based on preferences for health states, and are usually expressed on a continuum from perfect health (1) to death (0), although health states worse than death can also be evaluated (Russell 2008). Generic single index score instruments include the EuroQol-5D, Health Utilities Index Mark III, SF-6D (derived from RAND-36/SF-36), and the 15D.

2.3.2 HAQ

The Stanford Health Assessment Questionnaire (HAQ) was originally developed as one of the first self-report, functional status measures for use in RA patients and has become one of the most often used instruments in other musculoskeletal disorders, as well (Fries et al. 1980). Although the HAQ is not disease-specific, it was validated in RA patients.

The HAQ is a measure of physical disability that assesses a respondent's ability to complete everyday tasks in dressing and grooming, rising, eating, walking, personal hygiene, reach, grip and other activities. Each of these areas is assigned a section score that is further adjusted to account for the use of any aids or devices or any help from another person. These scores are then summed and averaged to give an overall score between 0.0 (best

possible function) to 3.0 (worst function). Besides the statistical significance of the results, the clinical importance of the results should also be reported to avoid over-reporting of conclusions (van Tulder et al. 2007). According to several studies, the minimally clinically important difference (MCID) of the HAQ in RA patients ranges from 0.09 to 0.19 (Pope et al. 2009, Kosinski et al. 2000, Marra et al. 2005).

The HAQ has been shown to be useful in studies of short-term response to treatment (Bruce and Fries 2003). Physical disability measured by the HAQ depends on the disease stage. In early RA, HAQ disability is influenced by disease activity and in late disease also by the irreversible joint damage. In RA of longer duration, therefore, the HAQ score is less responsive to change (Welsing et al. 2001, Aletaha and Ward 2006). The Finnish version of the HAQ has been available since the first half of 1990s (Hakala at al. 1994).

2.3.3 SF-36

The SF-36 is a well-validated generic health status measure used in health surveys in the general population as well as in various populations with different diseases. The 36 items in the questionnaire are grouped into 8 multi-item subscales measuring physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, mental health, and role limitation due to emotional problems. For each subscale a score is calculated with possible values from 0 to 100, where low scores indicate poor health (Ware and Sherbourne 1992). In a study by Kosinski et al. (2000), mean changes in the SF-36 domain scores were calculated for patients with RA at one level of improvement in patient-reported pain or global assessment of disease activity. For pain, these ranged from 1.9 to 10.8 and for global assessment of disease activity from 4.2 to 21.0. Earlier analyses have indicated that improvements of 5 to 10 points in SF-36 domains represent an MCID in RA patients (Wolfe et al. 2005).

SF-36 and the RAND 36-Item Health Survey 1.0 (RAND-36) contain identical items. However, their scoring algorithms to derive physical and mental health summary scores and the general health subscale, and scoring of the second pain item (interference with normal work) differ slightly (Cunningham et al. 2003).

2.3.4 15D

The 15D (Sintonen 2001) is a generic, 15-dimensional, standardised, self-administered measure of HRQoL that can serve both as a profile and as a single index score measure. The valuation system of the 15D is based on an application of the multiattribute utility theory. A set of utility or preference weights, elicited from representative samples of the general population through a 3-stage valuation procedure, is part of an additive aggregation formula to generate the utility score, i.e., the 15D score (single index number) covering all the dimensions. A change in score of ≥ 0.03 is considered clinically significant or important (Sintonen 1995). For most of the important properties, the 15D compares favourably with other instruments of its kind (Stavem 1999, Hawthorne et al. 2001, Sintonen 2001), and the instrument has thus been widely used in patients with different diseases in different countries.

2.4 Economic burden of rheumatic diseases

2.4.1 General

The economic burden of four major rheumatic diseases: OA, osteoporosis, RA, and low back pain, is substantial both for the individual but also for the health-care and social-care system. Musculoskeletal diseases are the most common cause of long-term pain and physical disability, and their prevalence is growing because of the increase in life expectancy and ageing populations. The burden of these diseases relates also to the cost of the disease to the health care system of the country (Reginster 2002, Woolf and Pfleger 2003).

In a systematic review of the literature, Cooper (2000) found that all reviewed studies reported the economic impact of RA to be substantial. The mean annual direct costs per person with RA were US $5 720 and indirect costs US $5 822. In most studies, costs were not uniformly distributed, with higher costs incurred by the patients with the worst RA. The strongest predictor of cost has been functional disability (Kavanaugh 2007).

2.4.2 Direct costs

Direct costs include the costs of medical care and related items. These include expenses for visits to doctors, laboratory and radiological examinations, hospital costs, medications, transportation to and from the doctors, and special aids (Lubeck 2003).

2.4.3 Indirect costs

Indirect costs are those resulting from lost function in one's usual activity, including work disability, sick leave or reduced productivity. In RA, the indirect costs, with the main components of sick leave, part-time work, and early retirement, can account for the major part of the general costs, ranging from 50 to 85% of all costs (Puolakka et al. 2004).

In calculating loss of productivity, the two methods commonly used are the human capital and the friction cost approaches. The human capital approach values the individual's productivity at its market price; this is the potential gross salary of the individual, including all of the employer's contributions, and for self-employed persons, the gross personal income including statutory insurance expenses (Johannesson 1996). The friction cost approach assumes that the disabled person is replaced by a currently unemployed person during a friction period (Lofland et al. 2001). The friction period is the time during which the sick person is replaced, and friction costs include all the expenses related to replacing that worker. The human capital approach takes a societal

approach, while the friction cost approach includes the costs to the employer for replacing the disabled worker.

2.4.4 Intangible costs

Intangible costs are defined as pain and suffering of a patient because of disease and include reduction in physical function, increased psychological distress, and reduced social function. Intangible costs can be measured either by the HRQoL questionnaires or alternatively by a contingent valuation method that is a stated preference method based on the “elicitation of levels of willingness to pay“ (Lubeck 2003, Xie et al. 2008).

2.5 Treatment of RA

2.5.1 General

The aim of RA treatment is not only to relieve symptoms and signs, but also to prevent destruction of joints. Several studies have shown that lower disease activity leads to less radiographic progression (Boers et al. 1997, Makinen et al. 2007). The goal of treatment should therefore be to induce remission. Thus far, no gold standard of remission criteria in RA patients is available. In clinical trials, the American Rheumatism Association (ARA) remission criteria (Pinals et al. 1981) or its modifications must serve. Another option is the Disease Activity Score with the 28-joint count (DAS28) and a cutpoint of <2.6 as a definition of remission in RA (Prevoo et al. 1995), although its use has led to criticism (Landewe et al. 2006).

2.5.2 Corticosteroids

Corticosteroids have been used for RA treatment since the invention of cortisone in the 1940s. Initial enthusiasm for corticosteroids because of their dramatic impact on suppressing the inflammation in RA patients ceased when their long-term side-effects emerged. Nowadays, the strategy of corticosteroid treatment includes three possibilities: step-down with a high initial dose later tapered off (Boers et al. 1997), bridge-therapy aimed at controlling symptoms in the period of high disease activity before newly started DMARDs start to have an effect (van Riel at al. 1999), or a long-term low-dose strategy of oral corticosteroids together with a single or a combination of DMARDs (Kirwan 1995). A recent review has presented ample evidence that low-dose corticosteroids together with DMARDs are able to reduce the rate of erosion progression in RA patients substantially (Kirwan et al. 2007). On the other hand, daily use of corticosteroids has caused the most problems with long-term toxicity such as cumulative effects on bone that lead to osteoporosis and other deleterious effects associated with increased mortality (Wolfe et al. 1994).

2.5.3 Traditional DMARDs

The cornerstone of RA treatment involves DMARDs either as monotherapy or in combinations, with or without corticosteroids. Different strategies of RA treatment with DMARDs have appeared during the last 20 years. The traditional “pyramid” approach included the use of DMARDs only as the last option after NSAIDs and corticosteroids had failed. The “sawtooth” strategy introduced by Fries (1990) included an earlier start of DMARDs, but these were changed sequentially only if the first drug failed (Mottonen et al. 1996, Fries et al. 1996). The traditional DMARDs begin to show a clinical effect only after 2 to 6 months of treatment. Therefore, those patients who failed the first DMARD had long periods without effective treatment before the second DMARD began to work (Aletaha and Smolen 2002).

The modern approach of RA treatment includes a very early start of treatment because even a delay of 4 months can affect long-term outcome of treatment (Lard et al. 2001). In a case-control, parallel-group study among patients who started DMARDs after a median disease duration of 3 months (early RA), 60% achieved an ACR50 response at 3 years compared with 25% of those who started DMARD treatment after a median disease duration of 12 months (late RA). In the late-RA group, the radiologic progression rate during a 3-year follow-up measured by the Larsen score was significantly higher than in the early-RA group (Nell et al. 2004).

During the last decade a strategy of initiating combination treatment with two or more DMARDs has become increasingly popular. The aim of combining DMARDs with different mechanisms of action is to increase efficacy while maintaining a favourable toxicity profile. At least two differing approaches of combination treatment exist: the step-down and the step-up strategies. In the step-down approach, the most aggressive treatment with combinations of DMARDs is used at baseline, and once the disease is under control, the drugs with the least favourable toxicity profile are withdrawn. In the step-up approach, the DMARDs are added one at a time until the disease is under

control, and therefore administration of multiple DMARDs can be avoided in patients who respond to a single DMARD.

Several studies of RA patients have compared monotherapy with different combinations of DMARDs. Depending on the choice of DMARDs and study design, the results have been contradictory. In early RA, the FIN-RACO and COBRA studies have shown that combination treatment results in a favourable outcome both clinically and radiologically compared to that with monotherapy (Mottonen et al. 1999, Boers et al. 1997). In patients with established RA, studies have demonstrated that for patients failing with MTX or any other single DMARD, combination treatment has been more effective than monotherapy (O'Dell et al. 1996 and 2002, Tugwell et al. 1995).

A recent systemic review and metaanalysis that compared MTX monotherapy to combination therapy with other non-biologic DMARDs concluded, however, that in DMARD-naïve patients the balance of efficacy/toxicity favours MTX monotherapy (Katchamart et al. 2008). But this metaanalysis had limitations due to the heterogeneity of studies. Many of the studies included a small number of patients, most studies used lower doses of MTX than in current practice, several used drugs that are not commonly used, and the outcome measures were inconsistently reported.

The drug of choice among DMARDS is MTX, which has the highest rate of continued long-term therapy. In an analysis by Pincus et al (1992), MTX was the only DMARD that was continued in more than 50% of patients for longer than 5 years. Among traditional DMARDs, sulphasalazine, hydroxychloroquine, leflunomide, cyclosporine and aurothiomalate are also still in use.

2.5.4 Biologicals

The discovery that the macrophage-derived proinflammatory cytokine TNF-α plays a central role in the pathogenesis of RA led to the introduction of TNF-inhibitors (Brennan et al. 1992). Starting from 1998, the TNF-inhibitors infliximab, etanercept, and adalimumab have been approved for the treatment of RA. In RCTs, responses to TNF-inhibitors—after failure of initial conventional DMARD—have been better than responses to conventional DMARD monotherapy (Lipsky et al. 2000, Weinblatt et al. 2003, Bathon et al. 2000). In early DMARD-naïve RA patients, TNF-inhibitors in combination with MTX have shown not only clinical efficacy but also a significantly better outcome in radiological progression, when compared to MTX alone (Breedveld et al. 2006, St Clair et al. 2004). The safety profile of TNF-inhibitors in long-term follow-up studies is favourable, with no increase in rates of serious adverse events (Weinblatt et al. 2006, Moreland et al. 2006). These long-term follow-up studies are, however, still limited to a length of 4 to 7 years because the TNF-inhibitors have been available only for the last decade, and much longer surveillance is necessary to confirm their safety.

In clinical practice, patients who fail to respond to the first TNF-inhibitor immediately after the treatment is started, who lose the response later, or who suffer an adverse event are often switched to a second TNF-inhibitor. Several small observational studies have demonstrated that switching to the second TNF-inhibitor can be a good option in the case of treatment failure or an adverse event with the first TNF-inhibitor (Buch et al. 2007, Hansen et al. 2004, Haraoui et al. 2004, van Vollenhoven et al. 2003). Data from a large register study showed that RA patients who were switched to a second TNF-inhibitor had a high continuation rate, with 73% of patients continuing treatment after a mean 15 months of follow-up, although among those who discontinued treatment, the reasons for stopping the second drug were related to the reasons for stopping the first (Hyrich et al. 2007). Drug survival for the second TNF-inhibitor after the switch is usually longer than for the first, although not as long as for those patients not switched (Hjardem et al. 2007).

Other biologicals that are approved for RA treatment are anakinra, an interleukin 1 (IL-1) inhibitor; abatacept, a selective co-stimulation modulator; and rituximab (RTX), a B-cell-depleting agent that binds specifically to the B-cell surface antigen CD20. In one RCT, the short-term efficacy and safety of anakinra has been favourable (Fleischmann et al. 2003), but in an observational study, only 14% of patients continued anakinra after 2 years, with most of the discontinuations caused by lack of efficacy (den Broeder et al. 2006). RTX in combination with MTX has proven to be more effective than placebo plus MTX in patients with RA who had an inadequate response to a TNF-inhibitor (Cohen et al. 2006). Another observational study showed RTX to be more effective than an alternative TNF-inhibitor after an inadequate response to the first TNF-inhibitor (Finckh et al. 2007). A recent study of abatacept in RA patients who had failed TNF-inhibitor treatment showed the new selective co-stimulation modulator to be clinically efficacious and to have an acceptable safety profile (Genovese et al. 2008).

Although the clinical efficacy of new biological compounds has been shown to be superior to placebo or MTX in patients with RA, they nevertheless have limited efficacy. In fact, only a small proportion of patients achieve 70% improvement according to ACR criteria, and remissions are rare. Based on RCTs, less than 20% of the ACR criteria is achievable for a number of patients (range, 28-58%) (Redlich et al. 2003). Therefore, a number of new compounds have been invented, and RCTs to compare new molecules with placebo in the treatment of RA are conducted (National Library of Medicine. URL: www.ClinicalTrials.gov).

2.5.5 Treatment of other inflammatory joint diseases

Both traditional DMARDs and biologicals are available in the treatment of other inflammatory joint diseases. In AS, the therapeutic options have long been limited to NSAIDs for symptom control and to sulphasalazine in patients with predominantly peripheral arthritis. Today the TNF-inhibitors have shown excellent clinical efficacy in patients with AS and other SPAs (Braun et al.

2005a, 2005b). The Assessment of the SpondyloArthritis International Society (ASAS) working group has recommended TNF-inhibitors if the patient has a definite AS diagnosis and has active disease for at least 4 weeks based on the BATH AS disease activity index (BASDAI). The decision must be based on expert opinion, and the AS must be refractory to at least two NSAIDs at full doses during 3 months, refractory to treatment with intra-articular steroids (if needed), and refractory— in patients with predominantly peripheral arthritis— to sulphasalazine (Braun et al. 2006). The effect of TNF-inhibitors on HRQoL can be even more evident in patients with AS than with RA (Heiberg et al. 2005).

In JIA, pharmacological treatment depends on subtype and has to run parallel to the non-pharmacological options such as physical and occupational therapy. Very important is the multidisciplinary team including an ophthalmologist, a dentist, a social worker, and a psychologist.

The initial symptomatic therapies in JIA include NSAIDs and intra-articular steroids. The more aggressive and earlier use of DMARDs has improved the prognosis of JIA during the last 10 years. The first choice among DMARDs in persistent and active arthritis is MTX because of its effectiveness and acceptable level of side-effects (Ravelli and Martini 2007). Several other DMARDs such as hydroxychloroquine, aurathiomalate, sulphasalazine, leflunomide, and cyclosporine are still in use. During the last decade, the introduction of biologicals has provided a very important option for JIA patients who have failed to improve when on conventional treatment with DMARDs.

In acute ReA, NSAIDs serve to suppress inflammation and pain in the joints. An acute infection requires antibiotics. Current evidence does not support the use of long-term antibiotics for the treatment of acute ReA (Kvien et al. 2004, Hannu et al. 2006). If NSAID treatment fails, then DMARDs can be used. Some reports suggest that biologicals can be effective also in chronic cases of ReA without reactivating the initiating infection (Brandt et al. 2002, Gill and Majithia 2008).

3. AIMS OF THE STUDY

The purpose of the study was to explore the HRQoL of patients with rheumatic diseases with special emphasis on RA patients and to evaluate the treatment of inflammatory joint diseases with biologicals in routine practice. The specific aims of the study were to examine:

1. the HRQoL of patients with various rheumatic diseases referred to a university clinic and to analyse the impact of 8-month routine treatment on the HRQoL of those patients. (I)

2. any change in HRQoL during treatment with etanercept and adalimumab in patients with RA in routine practice. (II)

3. the one-year costs of patients with chronic inflammatory joint diseases during infliximab treatment compared to costs incurred one year before infliximab. (III)

4. the clinical impact on RA patients when they switch from infliximab to etanercept. (IV)

4. PATIENTS AND METHODS

The study population comprised patients with various rheumatic diseases attending the Department of Rheumatology at Helsinki University Central Hospital, except for Study II, where data for patients from Lappeenranta Central Hospital were also used. For demographic and clinical characteristics of all the patients see Table 2. All patients gave their written informed consent to participate, and the local ethics committee approved the study protocols.

In Studies II to IV, TNF-inhibitors were started according to the Finnish national recommendations for prescribing biological agents for RA. These recommend that the patients should have failed treatment with a combination of DMARDs including MTX and a low dose of corticosteroids, and they 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 at least 30 mm/h or a C-reactive protein (CRP) of at least 28 mg/l, or both; and 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, the same recommendations were modified for clinical practice. The 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 MTX and a low dose of corticosteroids, and have an ESR of at least 30 mm/h or a CRP of at least 28 mg/l or both.

Table 2. Demographic and clinical characteristics of the study populations

	Study I	Study II	Study III	Study IV
N	295	97	96	49
Age, years, mean (SD)	54 (16)	52 (13)	48 (12)	54 (11)
Gender, female (%)	221 (75)	73 (75)	63 (66)	43 (88)
Duration of disease, years, mean (SD)	6 (10)	17 (10)	16 (10)	13 (9)
RA (%)	99 (33)	97 (100)	65 (68)	49 (100)
ReA (%)	22 (7)	0	8 (8)	0
Chronic SPAs (%)	43 (15)	0	12 (13)	0
Arthralgia (%)	47 (16)	0	0	0
OA (%)	44 (15)	0	0	0
Systemic rheumatic diseases (%)	17 (6)	0	0	0
JIA (%)	9 (3)	0	8 (8)	0
Other (%)	14 (5)	0	3 (3)	0

SD, standard deviation; RA, rheumatoid arthritis; ReA, reactive arthritis; SPAs, spondyloarthropathies; OA, osteoarthritis; JIA, juvenile idiopathic arthritis

Study I comprised 295 patients with various rheumatic diseases who had a new referral to the Department of Rheumatology of the Helsinki University Central Hospital from May 2002 until April 2003. The total number of patients receiving the questionnaires was 676, and 385 (57%) of them responded. Complete baseline and follow-up data were available for 295 patients. Those 90 (23%) who responded to the first but not to the follow-up questionnaire can be considered dropouts. We compared the available data of the included patients to data of excluded patients and found that the excluded patients were younger and had less OA and more fibromyalgia and arthralgia, but the numbers of RA patients in both groups were similar (Table 3). This study is a part of a large ongoing study of secondary health care in the Helsinki University Hospital, which started in March 2002 (Räsänen et al. 2005).

Table 3. Characteristics of the included and excluded patients. Modified and reprinted with permission from *Rheumatology International* (Laas et al. 2009b).

Characteristics	Included patients (N=295)	Excluded patients (N=381)
Gender, female (%)	222 (75)	265 (70)
Age, years, mean (SD)	53 (15)	48 (15)*
RA (%)	99 (34)	121 (32)
OA (%)	44 (15)	31 (8)
Arthralgia and fibromyalgia (%)	47 (16)	77 (20)
Chronic SPAs (%)	43 (14)	67 (18)
AS (%)	21 (7)	38 (10)
PSA (%)	16 (5)	25 (7)
Enteropathic arthritis (%)	6 (2)	4 (1)
JIA (%)	9 (3)	11 (3)
ReA (%)	22 (7)	19 (5)
Systemic rheumatic diseases (%)	17 (6)	17 (5)
Other (%)	14 (5)	32 (8)

* Statistically significant difference (p<0.001)

Abbreviations as in Table 2.

For analyses of HRQoL, the patients were divided into eight groups according to diagnosis: 99 RA, 44 OA, 47 arthralgia and fibromyalgia, 43 chronic SPAs (AS, PSA, enteropathic arthritis), 22 ReA, 17 systemic rheumatic diseases, 9 JIA, and 14 other.

To analyse in RA patients whether HRQoL was related to duration of disease, we made two groups according to disease duration: 47 patients with RA for 2 years or less as the early-RA group and 52 patients with RA over 2 years as the late-RA group.

For comparing the HRQoL of our study population with that of the general population, we used the general Finnish population data on HRQoL, as measured by the 15D, from the health examination survey "Health 2000" (Aromaa and Koskinen 2004).

Study II

In the second study, 97 RA patients who started treatment with adalimumab or etanercept at Helsinki University Central Hospital or at Lappeenranta Central Hospital during 2003-2006 were asked to participate. The choice of TNF-inhibitor was made on clinical grounds by the rheumatologist treating each patient. Adalimumab was given 40 mg subcutaneously every other week and etanercept 25 mg subcutaneously twice weekly. Patients were seen by the rheumatologist at baseline and 3 months after the first visit.

Study III comprised 96 patients with different arthritis diagnoses. Besides 65 patients with RA, 8 patients had chronic ReA, 8 JIA, 6 PSA, 6 AS, 2 adult-onset Still's disease, and one had SAPHO (Synovitis-Acne-Pustulosis-Hyperostosis-Osteomyelitis) syndrome. All patients were using DMARDs, 61% as monotherapy and 39% in various combinations. The majority (82%) were using corticosteroids. MTX was the most common DMARD either as monotherapy or in combinations.

Treatment with infliximab was started at 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. If the response was insufficient, the dose or the interval could be adjusted.

Study IV

In the fourth study, 49 patients with RA who were switched from infliximab to etanercept during 1999-2003 were recruited. Infliximab was discontinued because of failure to respond in 20 (42%) patients, adverse events in 6 (12%), and non-medical reasons in 23 (46%). We used the term “non-medical reasons” for patients who were switched to etanercept for their own convenience or to avoid visiting the hospital for infliximab infusions. Infliximab was used as described in Study III and etanercept as in Study II.

Follow-up and outcome analyses

Clinical evaluation

In Study I, clinical data, including ESR, CRP, use of DMARDs and oral corticosteroids, and interventions and consultations by health professionals, were gathered retrospectively from patient records. In Studies II to IV, a thorough clinical evaluation was conducted on the first visit. Disease activity was measured by tender-joint count (of 68), swollen-joint count (of 66), by patient’s and physician’s global assessment of disease activity on a visual analogue scale (VAS) ranging from 0 (no symptoms) to 10 (most severe disease), by patient’s assessment of pain on VAS from 0 to 10, and by ESR and CRP. In addition, demographic data included age, gender, disease duration, presence or absence of RF, and current use of DMARDs and corticosteroids. In all studies, functional status was evaluated with the Finnish version of the HAQ (Hakala et al. 1994). The disability index was calculated on a scale of 0 to 3, based on answers to the questionnaire.

In Study IV, DAS28 was used to compare clinical outcome with infliximab and etanercept. The individual patients’ DAS28 was calculated at baseline, at 3, 6, and 9 months, and at the last visit, based on data for 28 swollen and tender joints. The clinical benefit of etanercept as a second biological was compared between the three groups depending on reason for infliximab discontinuation.

HRQoL

In the first study, 15D was used to measure HRQoL. Patients filled in the 15D and HAQ questionnaires on average 28 (SD19) days before the first visit. After 8 months, all patients were sent the questionnaires again which they filled in on average 236 (SD28) days after the first visit.

In Study II, the RAND-36 was used to measure the HRQoL (Hays et al. 1993, Aalto et al. 1999). The patients filled in the questionnaires of the RAND-36 and HAQ at baseline and 3 months after the first visit.

Costs

In Study III, economic data came from case records for the year preceding the start of infliximab treatment (period I) and for the subsequent first infliximab treatment year (period II) also including data from patients discontinuing infliximab before a year had elapsed from start of treatment.

Medical costs

Medical costs included costs of visits to the outpatient clinic or day unit, and costs of inpatient stays and orthopaedic operations. We also calculated the costs of DMARDs and corticosteroids but omitted the costs of NSAIDs and other painkillers and drugs for nonrheumatic diseases, because information on the use of these drugs was often lacking from medical records. Nor was information on primary health care costs available. Because costs for aid appliances, transportation, rehabilitation, and assistive devices were excluded, we used the term “medical costs” instead of “direct costs”, referring to the most relevant medication costs.

Work disability costs

For estimation of lost productivity, the human capital approach (Johannesson 1996) was chosen. A person’s productivity was defined as the total costs to an employer including salary along with any supplementary social welfare expenses. In the case of self-employment, productivity was defined as

personal income plus any statutory health and pension insurance expenses. To calculate the work disability costs, we recorded patient's occupation, employment status, and number of days off work from case records, which included certificates documenting the patient's work incapacity for claims for a sickness or rehabilitation allowance or a disability pension. The rehabilitation allowance is a cash benefit for persons who go through medical or surgical interventions or for those who take part in a rehabilitation program 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 (http://www.stat.fi/til/pal_en.html). Because wages have 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.

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. In 39 patients who had retired before study entry we included only medical costs in the analyses because during the study period the disability costs remained unchanged.

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 came 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 a rheumatology ward in Helsinki. The costs of laboratory tests and investigations were included in the price of a visit in the outpatient clinic. In euros, the 2002 price of infliximab per 100 mg was €538.37. The cost of one

outpatient visit was €106. The usual cost of a day-unit visit was €436 and for an infliximab patient €1 430.

Statistical methods

The results are given as means and standard deviations (SD) for normally distributed continuous variables, medians and ranges, or as lower and upper quartiles and 95% confidence intervals (CI) for continuous variables with skewed distributions, and as percentages for categorical variables. For continuous variables, the significance of the differences between the groups was analysed by the independent samples t-test or the Mann-Whitney test. In Studies III and IV, analyses of clinical outcome were performed according to the last-observation-carried-forward method.

In Study I, the significance of the differences between before and after treatment scores was analysed with the Student's paired samples t-test or the Wilcoxon test. Correlation of the HRQoL change with that observed in the HAQ scores and with the ESR and CRP values was studied with Spearman correlation. The significance of differences in categorical variables between groups was analysed with the Chi-square or Fisher’s Exact Test.

In Study II, the between-group differences in change in the RAND-36 domains over the 3-month treatment period were compared by a bootstrap-type ANCOVA with the baseline measurement as a covariate and by a multivariate Hotelling-type permutation test. Changes within groups were analysed by applying a permutation test or a Hotelling-type permutation test to related samples. The effect size ("d") was calculated by the method for paired samples: mean baseline scores minus mean follow-up scores, divided by the pooled standard deviation; 95% CI were obtained by bias-corrected bootstrapping (5000 replications). The Finnish general population values for the eight RAND-36 domains were weighted to match the gender- and age distribution of the study population.

In Study III, the CIs for the means were obtained by bias-corrected bootstrapping (10 000 replications) because the cost data were skewed (Efron and Tibshirani 1993). 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.

In Study IV, the statistical significance between groups was evaluated by permutation-type tests (Monte Carlo *p*-value) or the Fisher-Freeman-Halton test. Statistical comparison of changes in DAS28 measurement was performed by permutation-type tests. Time-to-event analysis based on the product limit estimate (bootstrap estimation) was used to derive a 95% CI of the cumulative “drug survival” function. A log-rank test with exact *p*-values identified statistical differences between cumulative proportions.

5. RESULTS

5.1. HRQoL in patients with common rheumatic diseases referred to a university clinic (I)

The baseline clinical characteristics of the patients in different disease groups are in Table 4. The mean (SD) 15D score of all rheumatic patients improved significantly (p<0.001) from 0.822 (0.114) at baseline to 0.840 (0.119) at the 8-month follow-up. Both the baseline and the follow-up 15D scores were significantly lower than the HRQoL of the age-standardized general population (p<0.05). Of the 15 dimensions covered by 15D, significant differences between patients and the general population were found in 11 dimensions, and the largest difference was for the dimension of discomfort and symptoms (Fig. 1).

Discomfort and symptoms, a dimension of 15D, was the one most affected dimension in patients with rheumatic diseases. We therefore present the data of this dimension in Table 5 together with the HRQoL and HAQ results. The lowest baseline HRQoL was in patients with OA and chronic SPAs. In patients with RA and ReA the improvement in the HRQoL during the 8-month follow-up was statistically significant. A clinically important change was reported by patients with ReA and systemic rheumatic diseases but not by the RA patients. The poorest HAQ score both at baseline and also at follow-up was in patients with RA. The HAQ score improved significantly in patients with RA, arthralgia and fibromyalgia, and ReA.

Table 4. Baseline clinical characteristics of patients among disease groups. Modified and reprinted with permission from *Rheumatology International* (Laas et al. 2009b).

	Mean age, years (SD)	Number of female, (%)	Median disease duration, years (IQR)	Median ESR, mm/h (IQR)	Median CRP, mg/l (IQR)	Number of patients treated with DMARDs (%)
RA (n=99)	59 (15)	82 (83)	3 (0.8, 10)	21 (12, 40)	7 (0, 17)	34 (34)
OA (n=44)	62 (11)	33 (75)	1.5 (0.5, 5)	11 (6, 20)	0 (0, 8)	0
Arthralgia and fibromyalgia (n=47)	47 (14)	42 (89)	1 (0.5, 2)	10 (6, 18)	0 (0, 6)	1 (2)
Chronic SPAs (n=43)	47 (15)	25 (58)	5 (1, 11)	15 (7, 26)	6 (0, 14)	12 (28)
ReA (n=22)	45 (13)	15 (68)	0.4 (0.3, 1.6)	12 (7, 18)	1 (0, 7)	0
Systemic rheumatic diseases (n=17)	53 (17)	12 (71)	2 (0.4, 4)	23 (10, 41)	9 (0, 20)	3 (18)
JIA (n=9)	28 (8)	7 (78)	19 (16, 26)	10 (9, 17)	0 (0, 4)	4 (44)
Other (n=14)	57 (12)	6 (43)	6 (0.5, 8)	16 (6, 35)	8 (0, 17)	0

SD, standard deviation; IQR, interquartile range; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DMARDs, disease-modifying anti-rheumatic drugs; RA, rheumatoid arthritis; ReA, reactive arthritis; SPAs, spondyloarthropathies; OA, osteoarthritis; JIA, juvenile idiopathic arthritis

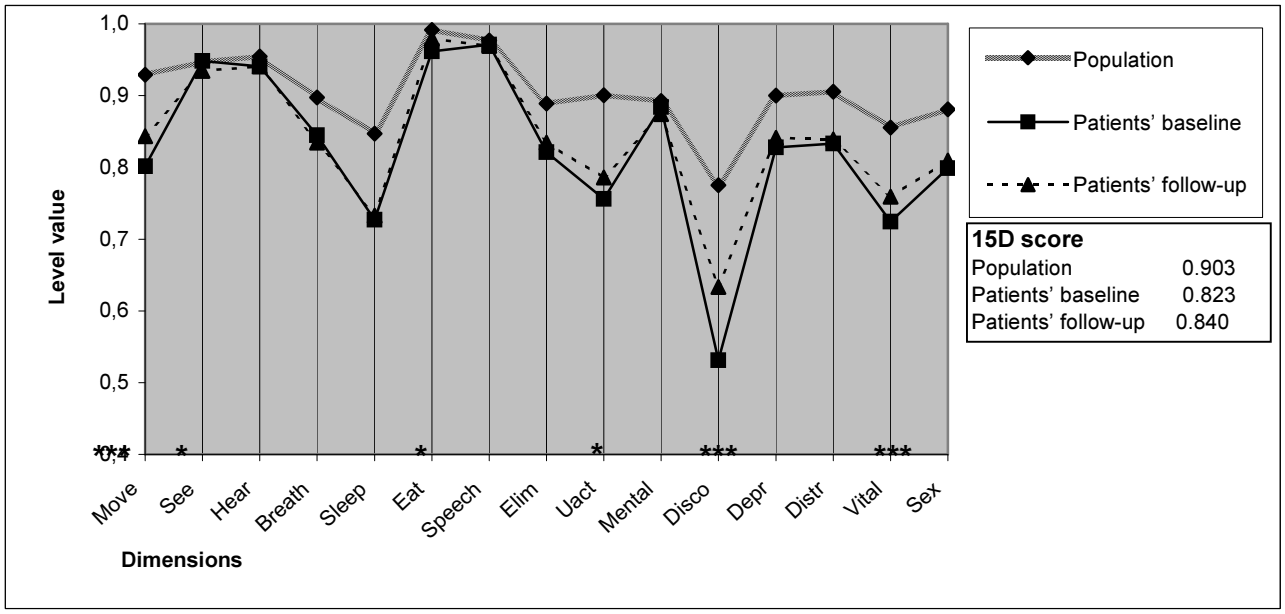

Figure 1. 15D profiles of patients with common rheumatic dieseases (n=295) at baseline and at 8-month follow-up compared to an age-standardized general population. (* denotes significant improvement from baseline at the $p<0.05$ level, and *** at the 0.001 level). The mean values are used. Modified and reprinted with permission from *Rheumatology International* (Laas et al. 2009b).

Table 5. Mean (SD) HRQoL (15D), discomfort and symptoms, and disability index of patients among diagnostic groups. Modified and reprinted with permission from *Rheumatology International* (Laas et al. 2009b).

Disease group	HRQoL (SD) at baseline	HRQoL (SD) at 8 months	Disco (SD) at baseline	Disco (SD) at 8 months	HAQ (SD) at baseline	HAQ (SD) at 8 months
RA (n=99)	0.815 (0.115)	0.840 (0.122)**	0.529 (0.228)	0.634 (0.218)***	0.843 (0.639)	0.623 (0.675)**
OA (n=44)	0.810 (0.103)	0.813 (0.114)	0.546 (0.181)	0.567 (0.213)	0.561 (0.518)	0.564 (0.529)
Arthralgia and fibromyalgia (n=47)	0.835 (0.094)	0.841 (0.113)	0.492 (0.182)	0.607 (0.238)***	0.474 (0.444)	0.360 (0.468)**
Chronic SPAs (n=43)	0.810 (0.133)	0.825 (0.137)	0.494 (0.247)	0.626 (0.249)**	0.457 (0.443)	0.383 (0.497)
ReA (n=22)	0.849 (0.112)	0.902 (0.083)**	0.518 (0.229)	0.720 (0.180)**	0.566 (0.655)	0.235 (0.448)*
Systemic rheumatic diseases (n=17)	0.843 (0.099)	0.880 (0.088)	0.582 (0.201)	0.700 (0.184)*	0.712 (0.565)	0.387 (0.476)
JIA (n=9)	0.928 (0.058)	0.927 (0.066)	0.801 (0.148)	0.900 (0.148)	0.232 (0.561)	0.196 (0.352)
Other (n=14)	0.787 (0.153)	0.770 (0.126)	0.533 (0.220)	0.557 (0.179)	0.510 (0.542)	0.614 (0.706)

HRQoL, health-related quality of life; SD, standard deviation; Disco, discomfort and symptoms; HAQ, Health Assessment Questionnaire. Other abbreviations as in Table 4. Changes statistically significant * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Besides visits to the rheumatologist, 127 (43%) patients also received treatment from or had a consultation with at least one member of the multidisciplinary team. Total number of visits and treatments was 244. Among the patient groups, 58% of patients with chronic SPAs, 55% with RA, and 46% with OA received multidisciplinary care. Of RA patients, 62% with early RA and 48% with late RA received multidisciplinary care. The provider of multidisciplinary care most frequently visited was the physiotherapist (Table 6).

Table 6. Multidisciplinary care in all rheumatic (n=295) and rheumatoid arthritis (RA) patients (n=99).

Type of multidisciplinary care	All patients number (%)	RA patients number (%)
Physiotherapist	77 (26)	34 (34)
Appliances	40 (14)	25 (25)
Occupational therapy	28 (10)	19 (19)
Social worker	18 (6)	12 (12)
Podotherapy	3 (1)	3 (3)
Rehabilitation program consultation	17 (6)	13 (13)
Rehabilitation at health center	34 (12)	6 (6)
Rehabilitation in inpatient facilities	2 (1)	1 (1)
Orthopedic surgeon consultation	18 (6)	11 (11)
Joint surgery	7 (2)	3 (3)

5.1.1 The HRQoL of patients with RA

Patients with RA had at baseline a significantly worse HRQoL than did the general population on the following dimensions: moving, breathing, sleeping, usual activities, discomfort and symptoms, depression, distress, and vitality (Figure 2). In 47 patients with early RA, the mean (SD) HRQoL improved during 8 months significantly from 0.813 (0.115) to 0.844 (0.141), $p<0.05$. This kind of improvement was not observed in 52 patients with late RA.

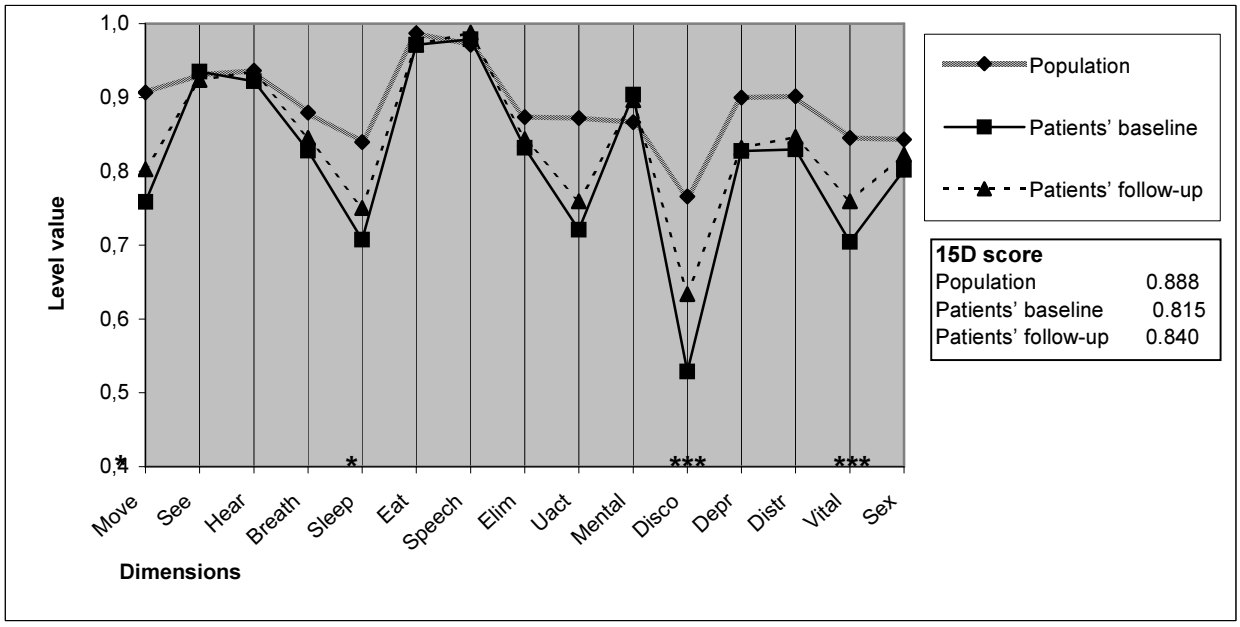

Figure 2. 15D profiles of RA patients (n=99) at baseline and at 8-month follow-up compared to an age-standardized general population. (* denotes significant improvement from baseline at the $p<0.05$ level, and *** at the 0.001 level). The mean values are used. Modified and reprinted with permission from *Rheumatology International* (Laas et al. 2009b).

At baseline, 34 (34%) patients with RA received treatment with DMARDs. Treatment with DMARDs or corticosteroids was started at the first visit in 58 DMARD-naïve RA patients. Only seven patients with RA were without any DMARD or corticosteroid treatment at follow-up (Table 7). In one patient, anti-TNF treatment was started in addition to DMARDs.

Table 7. DMARD and corticosteroid treatment of RA patients (n=99) at follow-up.

Variable	Number of patients	%
Drugs:		
Methotrexate	53	53
Hydroxychloroquine	35	35
Sulphasalazine	33	33
Gold salts, i.m. or p.o.	5	5
Podophyllotoxin	1	1
Leflunomide	1	1
Corticosteroids	30	30
Treatment strategy:		
Single DMARD therapy	36	37
Single DMARD therapy with corticosteroids	21	21
Combination DMARD therapy	6	6
Combination DMARD therapy with corticosteroids	25	25
Corticosteroids without DMARD therapy	4	4
No therapy	7	7

DMARDs, disease-modifying anti-rheumatic drugs; i.m., intra-muscular; p.o., per oral

5.2 Biologicals etanercept and adalimumab already improve HRQoL in patients with RA after 3 months of treatment (II)

In 97 patients with RA, the first biological treatment was started: in 58 patients with etanercept and in 39 with adalimumab. At baseline, 90 (93%) patients were using DMARDs with or without corticosteroids (Table 8). The clinical and demographic variables of the two study groups in the beginning of the study were comparable (Table 9).

The improvement in eight domains of the RAND-36 after 3 months of treatment was statistically significant both with etanercept (p=0.041) and with adalimumab (p=0.019) (Table 10). The two biologicals did not differ from each other regarding improvement in HRQoL (p=0.30). Both groups reported significant changes in the dimension of bodily pain. The etanercept group reported additionally a significant improvement in physical functioning, energy, social functioning, role functioning/emotional, and emotional well-being, but the adalimumab group only in general health.

The median (IQR) decrease in the HAQ in the etanercept group was 0.25 (0.12 ; 0.5) and in the adalimumab group 0.25 (0.13 ; 0.6), both of these changes were clinically important but only in the etanercept group did the improvement reach statistical significance. After 3 months of treatment, patients in both groups experienced clinically important and statistically significant improvements in all clinical variables (Table 11).

The largest differences in HRQoL between RA patients and the age- and gender-matched general population were in the physical domains of the RAND-36 both at baseline and after 3 months of treatment (Figure 3).

Table 8. DMARD and corticosteroid use at baseline with no statistically significant difference between groups. Modified and reprinted with permission from *Clinical and Experimental Rheumatology* (Laas et al. 2009a).

Variable	Etanercept n=58 (%)	Adalimumab n=39 (%)	All N=97
Drugs:			
Methotrexate	31 (53)	22 (56)	53 (55)
Hydroxychloroquine	18 (31)	11 (29)	29 (30)
Sulphasalazine	17 (29)	9 (23)	26 (27)
Podophyllotoxin	13 (22)	9 (24)	22 (23)
Leflunomide	11 (19)	11 (28)	22 (23)
Cyclosporine	10 (17)	6 (16)	16 (17)
Gold salts, i.m. or p.o.	4 (7)	3 (8)	7 (7)
Azathioprine	2 (3)	1 (3)	3 (3)
Corticosteroids	52 (76)	33 (75)	85 (76)
Treatment strategy:			
No drugs	1 (2)	0	1 (1)
Single DMARD	6 (10)	6 (15)	12 (12
Single DMARD with corticosteroids	10 (17)	10 (26)	20 (21)
Corticosteroids alone	6 (10)	2 (5)	8 (8)
Combination of DMARDs	7 (12)	2 (5)	9 (9)
Combination of DMARDs with corticosteroids	28 (48)	19 (49)	47 (48)

DMARDs, disease-modifying anti-rheumatic drugs; i.m., intra-muscular; p.o., per oral

Table 9. Baseline demographic and clinical characteristics of patients treated with etanercept or adalimumab with mean values (SD) or number of patients (percentages). Modified and reprinted with permission from *Clinical and Experimental Rheumatology* (Laas et al. 2009a).

Variable	Etanercept n=58	Adalimumab n=39	All n=97
Female (%)	74	76	75
Age, yrs (SD)	50 (14)	55 (11)	52 (13)
Duration of RA, years (range)	16 (1-47)	17 (1-37)	17 (1-47)
Seropositivity (%)	79	67	74
Number of tender joints, 0-68 (SD)	7 (5)	10 (7)	9 (6)
Number of swollen joints, 0-66 (SD)	11 (10)	12 (10)	11 (10)
Pain, VAS cm (SD)	6 (2)	6 (3)	6 (2)
Patient global assessment, VAS cm (SD)	6 (2)	6 (2)	6 (2)
Physician global, VAS cm (SD)	5 (2)	4 (2)	4 (2)
ESR, mm/h (SD)	43 (25)	38 (23)	40 (24)
CRP, mg/l (SD)	34 (5)	29 (7)	31 (24)
HAQ (SD)	1.22 (0.68)	1.14 (0.72)	1.18 (0.7)

SD, standard deviation; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RA, rheumatoid arthritis; VAS, visual analogue scale; HAQ, health assessment questionnaire

Table 10. RAND-36 domains at baseline and change in values after 3 months of treatment. Modified and reprinted with permission from *Clinical and Experimental Rheumatology* (Laas et al. 2009a).

Domain	Baseline		Change to month 3			
	Etanercept	Adalimumab	Etanercept	*p*-value	Adalimumab	*p*-value
	Mean (SD)	Mean (SD)	Mean (95% CI)		Mean (95% CI)	
Physical functioning (PF)	43.4 (25.6)	46.0 (26.8)	7.5 (3.0 to 12.0)	0.002	6.5 (-0.1 to 13.2)	0.056
Role physical (RP)	27.3 (38.2)	32.2 (37.2)	8.8 (-1.6 to 19.2)	0.12	1.8 (-10.4 to 14.0)	0.82
Pain (BP)	36.3 (17.8)	37.7 (19.9)	13.1 (7.6 to 18.6)	<0.001	13.9 (4.8 to 22.9)	0.003
General health (GH)	44.7 (22.0)	41.6 (16.8)	2.4 (-1.6 to 6.3)	0.24	7.3 (1.8 to 12.8)	0.011
Vitality (VT)	47.9 (23.4)	45.7 (24.2)	7.4 (2.1 to 12.8)	0.004	6.8 (-1.7 to 15.2)	0.11
Social functioning (SF)	61.2 (30.3)	65.2 (27.8)	9.2 (2.4 to 15.9)	0.013	2.7 (-8.3 to 13.7)	0.67
Role emotional (RE)	53.9 (46.5)	53.5 (44.2)	11.6 (0.7 to 22.6)	0.039	0.4 (-14.4 to 15.3)	0.92
Mental Health (MH)	68.4 (19.8)	67.3 (19.3)	3.7 (-0.4 to 7.7)	0.073	2.3 (-4.9 to 9.6)	0.52

SD, standard deviation; CI, confidence interval

Table 11. Change in clinical parameters from baseline to 3 months: median (IQR). All changes statistically significant. Modified and reprinted with permission from *Clinical and Experimental Rheumatology* (Laas et al. 2009a).

	Etanercept n=58	Adalimumab n=39	All n=97
Number of tender joints (0- 68)	4 (2; 10)	5 (2; 9)	5 (2; 10)
Number of swollen joints (0-66)	3 (2; 7)	5 (2; 11)	4 (2; 8)
Pain (VAS, cm)	2 (2; 4)	2 (1; 5)	2 (1; 4)
Patient's global assessment (VAS, cm)	3 (1; 4)	3 (2; 5)	3 (1; 4)
Physician's global assessment (VAS, cm)	2 (1; 3)	3 (1; 4)	2 (1; 3)
ESR, mm/h	10 (3; 30)	10 (6; 26)	10 (5; 27)
CRP, mg/l	10 (3; 30)	20 (7; 32)	14 (4; 30)

IQR, interquartile range; VAS, visual analogue scale, ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

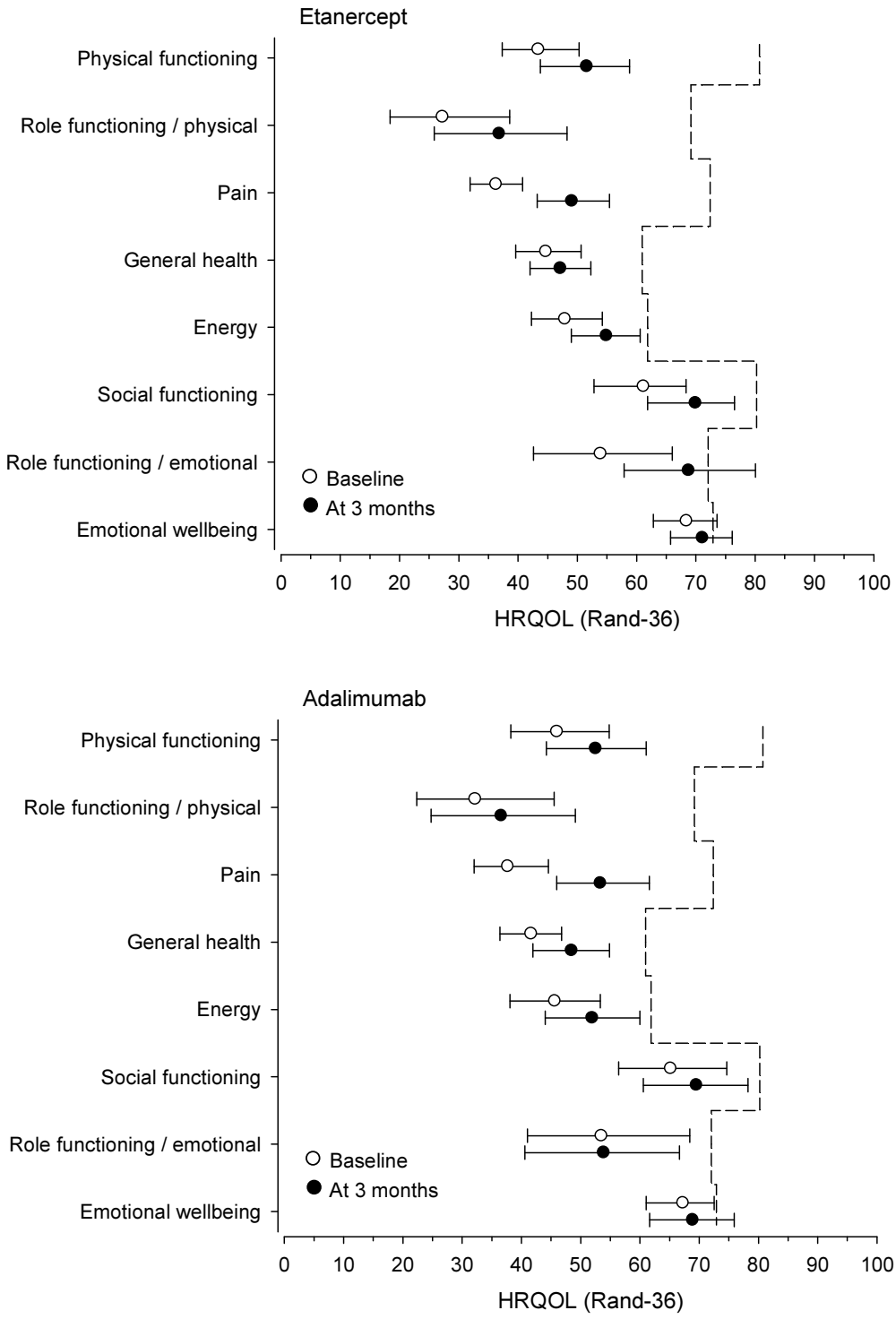

Figure 3 RAND-36 domains of treatment groups at baseline and at 3 months compared to an age- and gender-matched general population (---). Modified and reprinted with permission from *Clinical and Experimental Rheumatology* (Laas et al. 2009a).

5.3 Clinical outcome and costs of treating chronic arthritis patients with infliximab for one year (III)

5.3.1 Clinical outcome

In 96 patients with different types of chronic arthritis who had failed to improve with combinations of DMARDs including MTX and corticosteroids, infliximab was started. Baseline demographic characteristics in different disease groups appear in Table 12. The improvement in all clinical variables during one year of infliximab treatment was statistically significant compared to baseline (Table 13). The median (IQR) improvement in HAQ score was 0.56 (0.81; 0.25), and this is also clinically significant. A total of 22 patients discontinued infliximab before one year, 14 because of failure to respond by > ACR 50%, 4 because of adverse events, and 4 for other reasons. The adverse events were allergic reactions in three patients and lupus-like dermatitis in one patient.

Table 12. Baseline demographic characteristics of patients among disease groups, with means (SD) or percentages.

Variables	RA n=65	ReA n=8	JIA n=8	SPA n=6	PSA n=6	Still n=2	Sapho n=1
Age, yrs (SD)	51 (11)	43 (9)	34 (7)	48 (14)	43 (10)	27 (5)	51 (0)
Number of female, %	77	38	63	33	17	50	100
Disease duration, yrs (SD)	14 (9)	15 (6)	26 (12)	22 (12)	12 (6)	14 (15)	3 (0)
Retired patients, %	48	50	63	50	17	0	100
Discontinuing patients, %	26	38	0	17	0	50	0

RA, rheumatoid arthritis; ReA, reactive arthritis; JIA, juvenile idiopathic arthritis; SPA, spondyloarthropathy; PSA, psoriatic arthritis; SD, standard deviation

Table 13. Change in clinical variables during the second study year (period II) for all 96 patients. By analysis based on intention to treat by a last-observation carried-forward method, the statistical significance for each comparison was at the $p<0.001$ level. Modified and reprinted with permission from *Annals of the Rheumatic Diseases* (Laas et al. 2006).

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

† Hodges-Lehmann estimates of median difference

IQR, interquartile range; VAS, visual analogue scale; HAQ, Stanford Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

5.3.2 Costs

During period II, the number of day-ward and rheumatology department visits increased, and the number of out-patient visits decreased (Table 14). The number of admissions to other wards and orthopaedic operations during both periods were comparable.

Table 14. Number of visits per patient (n=96) during one year prior to (period I) and during one year after institution of infliximab (period II).

	Period I		Period II	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Number of outpatient visits	4.6 (2.8)	4 (3; 6)	0.3 (1.2)	0
Number of hospital admissions to rheumatology ward	0.6 (0.9)	0 (0; 1)	1.5 (2.4)	0 (0; 2)
Number of day-ward visits	2.3 (1.9)	1 (1; 4)	8.3 (1.8)	8 (8; 10)
Number of hospital admissions to other wards	0.4 (0.2)	0	0.1 (0.3)	0
Number of orthopaedic operations	0.2 (0.5)	0	0.3 (0.5)	0

SD, standard deviation; IQR, interquartile range

Medical costs increased during period II by €12 015 (95% CI, 6 496 to 18 076) per patient compared to period I. The costs rose due to visits for infliximab infusions either in the day-ward or in the rheumatology department (Table 15).

The mean drug cost of 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, a slight decrease occurred in the costs of outpatient visits, conventional DMARDs, and corticosteroids. Those 22 patients who discontinued infliximab prior to one year were responsible for 58% of hospital admission costs not related to infliximab administration in period II. After infliximab discontinuation, those patients needed hospitalisation either for treatment of adverse events or because of RA severity. The total costs for patients with RA were higher than for patients with non-RA during both periods, but the difference in costs was not statistically significant (Table 16).

Table 15. Medical costs per patient during one year prior to (period I) and one year after institution of infliximab (period II). Reprinted and modified with permission from *Annals of the Rheumatic Diseases* (Laas et al. 2006).

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 hospitalisations in rheumatology ward	6 526 (4 094 to 10 756)	9 662 (6 384 to 14 449) §	3 136 (1 575 to 7508)
Costs of day-ward visits	327 (222 to 500)	9 547 (8 786 to 10 317) §	9 220 (8 482 to 9 976)
Cost of drugs (DMARDs and corticosteroids)	1 861 (1 592 to 2 166)	952 (755 to 1 227)	-903 (-1 167 to -672)
Costs of hospitalisations in other wards	199 (26 to 970)	662 (205 to 1 923)	463 (-105 to 1 530)
Costs of orthopaedic surgery	3 536 (1 988 to 5 760)	4 070 (1 656 to 6 484)	534 (-2 132 to 4 058)
Total costs	12 920 (10 031 to 17 416)	24 935 (20 699 to 31 874) §	12 015 (6 496 to 18 076)

† CI 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 anti-rheumatic drug

Table 16. Total costs per patient during one year prior to (period I) and one year after initiation of infliximab (period II) in patients with RA and in patients with other diagnoses (Non-RA). Median values (IQR).

Costs, €	RA patients, n=65	Non-RA patients, n=31	All patients, n=96
Period I	5 644 (2 766, 13 469)	4 933 (2 625, 18 175)	5 418 (2 721, 13 489)
Period II	14 187 (12 183, 23 945)	14 018 (11 771, 22 798)	14 102 (11 933, 22 996)

RA, rheumatoid arthritis; IQR, interquartile range

At the start of infliximab infusions, 49% of patients were working full-time and 4% half-time; 41% were retired because of work disability, and 6% were retired as being over 63. Mean work disability costs for those 51 patients available for the active work force decreased by €130 (95% CI : -1 268 to 1 072) during period II. At the same time, the mean number of days off work on short-term sick-leave or rehabilitation allowance increased from 121 during period I to 141 during period II. In addition, 11 patients during period I and 12 patients during period II were on a rehabilitation allowance.

5.4 Clinical impact of switching from infliximab to etanercept in patients with RA (IV)

5.4.1 Baseline characteristics of patients

Altogether 49 patients with RA were switched from infliximab to etanercept treatment, and they were divided into three groups according to the reason for the switch: 20 patients because of infliximab failure, 6 because of an adverse event, and 23 for some non-medical reason.

At baseline, clinical characteristics of patients in the groups did not differ from each other with only the exception of infliximab-treatment duration (Table 17). All patients were using DMARDs, and 88% used corticosteroids. MTX was the most common DMARD either as monotherapy or in combinations (Table 18). Drug survival for infliximab differed between the groups infliximab failure, adverse event, and non-medical reason (Figure 4).

5.4.2 Safety of switching from infliximab to etanercept

Etanercept was discontinued in 20 cases: for lack of efficacy in 12 cases and adverse events in 7. One patient died, the cause of death being complications after hip fracture. The adverse events included: allergic reactions in three, infections in two, demyelinating neuropathy in one, and subjective symptoms (subfebrile fever, head ache) in one patient. No patient developed tuberculosis, a possible TNF-inhibitor associated infection. One patient with an allergic skin rash during infliximab had a similar rash after 4 months of etanercept and thus had to discontinue the treatment. The mean (SD) time to discontinuation of etanercept was 4 (2) months (Figure 5).

Table 17. Baseline clinical characteristics of 49 patients grouped according to reasons for switching from infliximab to etanercept. Reprinted and modified with permission from *Clinical Rheumatology* (Laas et al. 2008).

Characteristics	Infliximab failure (N=20)	Adverse event (N=6)	Non-medical reason (N=23)	*p*-value
Number of female (%)	15 (75)	6 (100)	22 (96)	0.09
Age, years, mean (SD)	51 (12)	56 (11)	50 (10)	0.51
Seropositivity (%)	13 (65)	5 (83)	14 (61)	0.77
Duration of disease, years, median, (range)	8 (1-32)	12 (5-26)	16 (3-38)	0.06
Duration of infliximab, months, median (range)	16 (1-32)	6 (1-32)	27 (10-44)	<0.001
Number of previous DMARDs, median (range)	6 (3-10)	7 (5-8)	7 (3-8)	0.95

SD, standard deviation; DMARD, disease-modifying anti-rheumatic drug

Table 18. Use of DMARDs and corticosteroids at the introduction of infliximab

Therapy	Infliximab failure N (%)	Adverse event N (%)	Non-medical reason N (%)
Drugs			
Methotrexate	12 (60)	3 (50)	17 (74)
Gold salts, i.m. or p.o.	2 (10)	0	2 (8)
Hydroxychloroquine	2 (10)	1 (17)	4 (17)
Azathioprine	1 (5)	0	3 (13)
Leflunomide	7 (35)	1 (17)	2 (9)
Sulphasalazine	3 (15)	0	1 (4)
Cyclosporine	1 (5)	2 (33)	3 (13)
Podophyllotoxin	1 (5)	2 (33)	5 (22)
Corticosteroids	19 (95)	5 (83)	19 (83)
Strategy			
Single therapy	1 (5)	1 (17)	2 (9)
Single therapy with corticosteroids	13 (65)	2 (33)	11 (48)
Combination therapy	0	0	2 (9)
Combination therapy with corticosteroids	6 (30)	3 (50)	8 (34)

DMARD, disease-modifying anti-rheumatic drug; i.m., intra-muscular; p.o., per oral

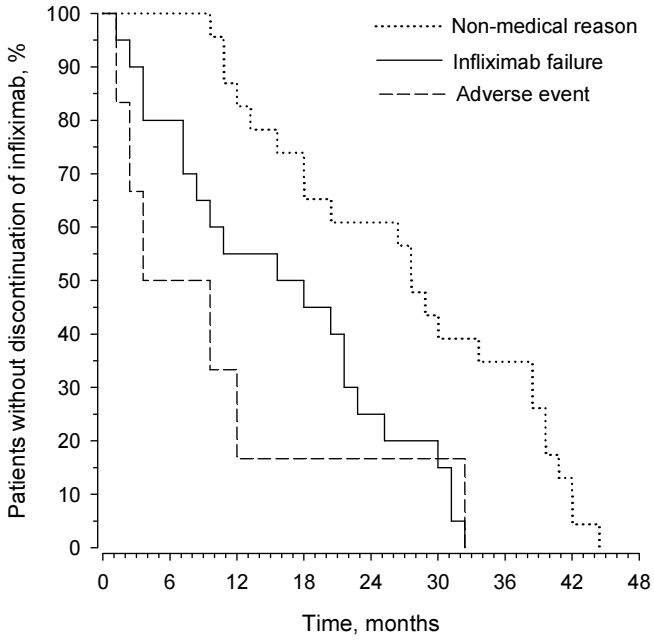

Figure 4. Drug survival for infliximab in groups according to reasons for switching from infliximab to etanercept. Reprinted with permission from *Clinical Rheumatology* (Laas et al. 2008).

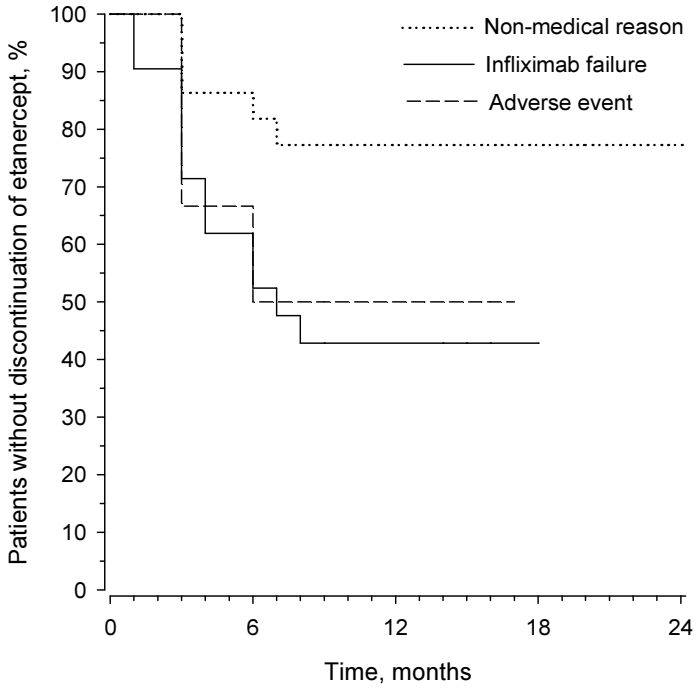

Figure 5. Drug survival for etanercept in groups according to reasons for switching from infliximab to etanercept. Reprinted with permission from *Clinical Rheumatology* (Laas et al. 2008).

5.4.3 Clinical outcome of switching from infliximab to etanercept

In the non-medical-reasons group, the mean (SD) DAS28 before switching from infliximab to etanercept treatment was 2.61 (0.9); this increased slightly after switching, by 0.38 (95% CI, -0.12 to 0.95), statistically not significantly (*p*=0.136). The mean (SD) DAS28 before switching in the infliximab failure group was 5.49 (1.4) and in the adverse event group 5.06 (1.4). After switching, a statistically significant decrease in the DAS28 appeared in both groups: -1.19 (95% CI, -2.14 to –0.31, *p*=0.023) in the infliximab failure group; and -1.30 (95% CI, -2.32 to –0.32, *p*=0.048) in the adverse event group (Figure 6).

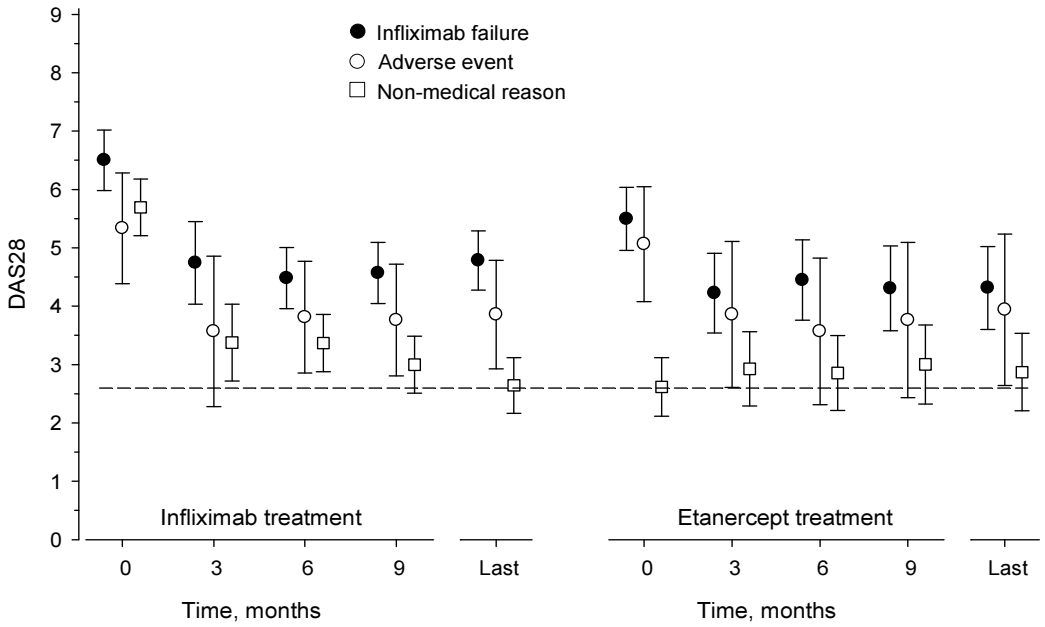

Figure 6. Clinical outcome during infliximab and etanercept treatment based on DAS28 in groups according to reasons for switching from infliximab to etanercept. Proposed remission cut-off point of DAS28 at 2.6 (---). Reprinted and modified with permission from *Clinical Rheumatology* (Laas et al. 2008).

6. DISCUSSION

6.1 HRQoL in patients with common rheumatic diseases

The 295 patients referred to the rheumatology clinic had a significantly lower baseline HRQoL than did the age-standardized general population. Analyses of HRQoL among disease groups revealed that the poorest HRQoL was in patients with OA and SPA and the poorest HAQ disability index ratings in patients with RA. Treatment adjustments improved statistically significantly the HRQoL of patients with RA and ReA, and an improvement in HAQ was observable in patients with RA, arthralgia and fibromyalgia, and ReA. A clinically important change of more than 0.03 units in 15D was reported by patients with ReA and systemic rheumatic diseases but not by those with RA. The dimension of the 15D most affected, discomfort and symptoms, improved in all patients except in those with OA and JIA.

In our study, only one patient with RA received anti-TNF treatment, whereas most of the patients had a single or a combination of DMARDs. Improvement of HRQoL may be even greater with the use of anti-TNF treatments (Kimel et al. 2008, van der Heijde et al. 2005).

Patients with musculoskeletal disorders have had a poorer HRQoL than those with other chronic diseases (Sprangers et al. 2000, Alonso et al. 2004, Loza et al. 2008). Poor HRQoL is associated with the dimensions of pain and physical functioning (Reginster 2002). One population-based cohort study showed that patients with OA of the hip or knee, RA, osteoporosis, or fibromyalgia reported the worst HRQoL (Picavet and Hoeymans 2004). Our results are in line with those findings.

Patients with RA had a significantly lower HRQoL at baseline and at follow-up than did the age-adjusted general population. The dimensions of 15D most affected were those associated with physical functioning: moving, usual activities, discomfort and symptoms, but also those associated with mental

functioning: sleeping, depression, distress, and vitality. These findings are in accordance with earlier ones in regard to HRQoL in patients with RA (Uhlig et al. 2007, Chorus et al. 2003). In our study, patients with early RA experienced statistically significant improvement in their HRQoL, whereas those with late RA failed to improve significantly. Similarly, studies of early arthritis have shown that treatment can restore the HRQoL when started in the early disease phase. In a registry study from northern Sweden, the HRQoL of patients with recent-onset RA (< 1 year) improved both statistically and clinically significantly during a 24-month follow-up (West and Jonsson 2005). In a RCT of early RA patients (< 3 years) treated either with etanercept or MTX, the 52-week improvement in HRQoL for both treatment groups was statistically significant (Kosinski et al. 2002).

The HRQoL of patients in the chronic SPA group was one of the poorest and failed to improve during 8 months of follow-up. Earlier studies showed that patients with psoriatic arthritis and ankylosing spondylitis have a lower HRQoL than does the general population, one that can be as low as the HRQoL in RA patients (Husted et al. 2001, Zink et al. 2006). Several RCTs of anti-TNF treatments in AS patients focusing on HRQoL have shown a good clinical response and a statistically significant improvement (Han et al. 2007, Davis et al. 2005).

Patients with ReA reported in our study significant improvement both in their HAQ level and their HRQoL that can be explained – besides as good treatment effect – also by the natural course of the disease. ReA can resolve spontaneously during 3 to 12 months or progress to chronic disease. Only 15 to 20% of patients develop chronic disabling symptoms (Wu & Schwartz 2008).

Our patients with OA had a short median (IQR) disease duration of 1.5 (0.5; 5) years but one of the lowest HRQoL scores. In accordance with this, an HRQoL study of patients with symptomatic hand OA or RA showed that both groups had lower HRQoL scores than did healthy controls. Hand OA patients had SF-36 scores similar to those of RA patients as to pain, vitality, and social

functioning but better scores in measures of physical health (Slatkowsky-Christensen et al. 2007). Another study of OA patients in a primary care setting concluded that patients with OA are less limited in their mobility but appear to suffer from an equivalent pain intensity as do patients with RA (Rosemann et al. 2007).

We found that conservative treatment failed to improve the HRQoL of OA patients in 8 months of follow-up. This is in accordance with the natural course of OA that can have a progression rate of 4% per year (Felson et al. 1995). The pharmacological treatment of OA patients includes NSAIDs and glucosamine products. A recent Cochrane review on the effectiveness of glucosamine in OA patients showed a 28% improvement in pain (change from baseline) and a 21% improvement in function based on the Lequesne index; the results of different studies were, however, not uniformly positive (Towheed et al. 2005). The same review failed to show improvement in the pain, function, and stiffness index of the Western Ontario and MacMaster Universities OA Index (WOMAC) that is an OA-specific health status instrument (Bellamy et al. 1988). On the other hand, RCTs of NSAIDs have shown at least short-term improvement in HRQoL of OA patients (Lisse et al. 2001, Zhao et al. 1999). A risk for serious adverse events, however, limits the long-term use of NSAIDs. The only treatment method that has shown a significant improvement in HRQoL in OA patients is hip or knee joint replacement (Norman-Taylor et al. 1996, Escobar et al. 2007).

6.2 Early improvement in the HRQoL of RA patients during their first anti-TNF treatment

The HRQoL of our RA patients had already improved significantly after 12 weeks of treatment with etanercept or adalimumab. Improvement in HRQoL with both biologicals was equal and paralleled clinical outcome variables.

Several RCTs have assessed the HRQoL of RA patients in subgroup analyses. In an RCT of etanercept, HRQoL was measured with the SF-36 in a

subgroup of 48 RA patients, with the scores for physical and mental components calculated. Both scores improved significantly after 26 weeks of treatment with etanercept 25 mg twice weekly (Mathias et al. 2000). Exactly the same follow-up time was used in RCT of adalimumab, where again significant improvement in HRQoL was observable (Mittendorf et al. 2007). A recent study of patients with early RA treated with adalimumab already showed improvement in physical domains of the SF-36 after 12 weeks of treatment (Kimel et al. 2008). In our study of adalimumab and etanercept, our follow-up time was identical, but the patients had long-standing severe RA and were treated in routine practice. Despite this we were able to demonstrate rapid improvement in HRQoL as measured by RAND-36.

In longitudinal studies of RA patients treated with DMARDs, the HAQ has shown a tendency toward a slight increase with time. In a 5-year follow-up study of 863 RA patients and 1176 population controls, the increase in HAQ in both groups was 0.01 units per year, an increase primarily attributable to the age-group over 70 (Sokka et al. 2006). In our study of RA patients treated with biologicals, their HAQ scores improved statistically significantly in the etanercept group with a median (IQR) change of 0.25 (0.12 to 0.5). In the adalimumab group the improvement of the HAQ by 0.25 (0.13; 0.6) was not statistically significant, but the change was clinically important. In a study of pooled data of 36 trials (Aletaha and Ward 2006), authors showed that patients with late RA show less improvement in the HAQ as response to treatment than do patients with early RA. They explained the lesser improvement in disability by the irreversible nature of joint damage. Therefore, we assume that the HAQ results of our study of patients with long-standing RA would have been even better had biologicals been started during its early phase.

Etanercept and adalimumab were equally effective in our RA patients in improving their HRQoL and clinical variables. The best way to compare the efficacy of two biologicals would be a randomized head-to-head study. Until now, no such study has been performed, so observational studies may be the only source of information for that kind of comparison. A recent register study

compared the effectiveness and medication costs of three biologicals: infliximab, etanercept, and adalimumab given in routine settings (Kievit et al. 2008). The authors concluded that improvements in the physical component scale of SF-36 and in DAS-28 were statistically more pronounced in patients treated with adalimumab and etanercept than in those treated with infliximab. One possible reason for the worse outcome of patients treated with infliximab was the use of the lowest possible dose, 3 mg/kg, in 80% of these patients. At the same time, treatment with infliximab resulted in higher medication costs. Etanercept and adalimumab were equally effective in improving the SF-36 physical scale, paralleling our own results.

6.3 Clinical outcome and costs of treating chronic arthritis patients with infliximab

We showed that treatment with infliximab improves the clinical outcome of patients with chronic arthritis significantly in routine clinical practice. On the other hand, infliximab raised medical costs substantially, and work disability costs failed to decrease.

Only a few studies have analysed the costs of using biological drugs in routine practice. Our results differ from those of a study conducted in southern Sweden (Kobelt et al. 2004) with 160 RA patients treated either with etanercept or infliximab in which the direct costs fell by 40% during the first year. Several differences between our studies should be noted. First of all, in the Swedish study the costs of those 44 patients who discontinued before completing one year of treatment were excluded from the direct costs, as were also the costs of biologicals. In our study both of those costs are included in the analyses. In addition, in the Swedish study, 70% of patients were treated with etanercept, which is associated with lower administration costs than is infliximab. All of our patients were treated with infliximab. The total costs increased in the Swedish study by €12 183 (44%), rising from a mean of €27 447 to €39 630; this is comparable to our figures. As expected, in neither of the studies did the indirect costs change during one year of follow-

up. This can be explained by severity of RA, long disease duration, short follow-up, and by the fact that approximately 50% of the Swedish patients and ours were already on long-term sick-leave (Kobelt et al. 2004). A recent study by Kievit et *al* (2008) evaluated the clinical outcome and medication costs of patients treated with infliximab, etanercept, and adalimumab. This register-based study showed that the medication costs of patients treated with infliximab were significantly higher than in patients treated with etanercept and adalimumab (Kievit et al. 2008).

Another approach to study the costs of biologicals is to use various models in the calculations. Such is the Dutch study by Nuijten et *al* (2001), in which the medical costs of patients treated with etanercept or infliximab were compared in a model. They concluded that etanercept was, from a health economics standpoint, superior to infliximab. But we have to take into account that the perspective of this study was that of Dutch society, and results of economic modeling studies cannot be easily transferred to other societies (Welte et al. 2004).

The reasons for higher costs for patients treated with infliximab can be the route of administration and the loading dose. Administration of infliximab intravenously requires visits to a medical specialist, while etanercept and adalimumab can be injected at home. In addition, infliximab treatment is started with a loading dose that raises the costs in the first year of use. For us, as well, costs for infliximab administration in addition to the price of infliximab raised the medical costs substantially.

6.4 Clinical impact of switching from infliximab to etanercept in patients with RA

In 49 RA patients, treatment with infliximab was discontinued and etanercept started for three reasons: infliximab failure, adverse event, or non-medical reasons. We were able to demonstrate that switching from established infliximab therapy to etanercept in the non-medical-reasons group was well

tolerated, and the good response was maintained. A similar result occurred with switching from infliximab to adalimumab in RA patients who have responded well to infliximab in a small open-label study in Ireland (Walsh et al. 2007). This was a study of 19 patients who were treated with infliximab for at least 12 weeks and responded to the treatment well; they were willing to switch to treatment with self-administered injections of adalimumab. The authors concluded that switching to adalimumab was safe and well tolerated and no significant changes in the HRQoL or physical function were detectable after the switch.

Although switching between etanercept, adalimumab, and infliximab has not been studied in any RCTs, several small observational studies have shown that, in the case of infliximab failure or adverse event, switching RA patients between biologicals can be an effective and safe option (Buch et al. 2007, Nikas et al. 2006, van Vollenhoven et al. 2003, Haraoui et al. 2004, Sanmarti et al. 2004, Hansen et al. 2004, Wick et al. 2005, Cohen et al. 2005). In our study, as well, the DAS28 score improved significantly in those whose reason to switch from infliximab to etanercept was infliximab failure or adverse event.

Several large register-based studies on treatment of RA patients with TNF-inhibitors have appeared lately. A recent study from the South Swedish Arthritis Treatment Group Register demonstrated that the response rates of the first-time anti-TNF switchers were lower than the response rates in anti-TNF-naïve patients, and furthermore, that the response rates of second-time switchers were markedly lower. They also showed that younger age, lower HAQ score, and higher DAS28 at baseline predicted better response to second-line treatment (Karlsson et al. 2008).

In a large prospective cohort study, 73% of patients who switched to a second anti-TNF agent had remained on the new therapy by the end of the mean follow-up of 6 months (Hyrich et al. 2007). Another register-based study reported that the drug survival rate after the switch to a second anti-TNF is significantly lower than for the first course of anti-TNF, and that drug survival was statistically significantly lower for infliximab (34%) than for etanercept

(76%), or adalimumab (67%) (Gomez-Reino et al. 2006). The second anti-TNF survival in our study was significantly lower than in the earlier studies. In the group of infliximab failure, the 1-year drug survival was 43% (95% CI, 26 to 70) and in the adverse event group 50% (95% CI, 33 to 100). Only in the group involving non-medical reasons was the 1-year drug survival after the switch higher, 77% (95% CI, 62 to 97).

A new approach for treating patients with an inadequate response to TNF-inhibitors is to switch to B-cell-depleting therapy with rituximab (RTX). This was assessed in a cohort study of 116 RA patients who had an inadequate response to at least 1 TNF-inhibitor and in whom switching to an alternative TNF-inhibitor was compared with switching to RTX (Finckh et al. 2007). Compared to those 66 patients who received another course of TNF-inhibitor, the evolution of DAS28 in those 50 patients who received RTX was more favourable (p=0.01). The authors concluded that treatment with RTX could be a better alternative in patients with a first or second inadequate response to a TNF-inhibitor than the use of all other alternative TNF-inhibitors. In addition, that study showed that one of the predictors of favourable outcome was the use of concomitant DMARDs.

In Studies I and II, we used the questionnaires RAND-36, 15D, and HAQ to measure patient-reported outcomes of treatment. Patient questionnaires have proven better than any laboratory test or imaging method in predicting important clinical outcomes of RA such as mortality and work disability (Pincus et al. 1984, Wolfe & Hawley 1998). They could therefore prove useful not only in clinical research but also for patient follow-up in routine practice. However, these questionnaires are so long and complicated that in the busy schedule of routine visits they are rarely used. Several shorter and easier questionnaires based on the HAQ have been developed in recent years such as the modified HAQ (MHAQ), multidimensional HAQ (MDHAQ), HAQ-II, and Routine Assessment of Patient Index Data 3 (RAPID3) that could be incorporated into the routine follow-up of individual patients (Pincus et al. 2005, 2008, Wolfe et al. 2004).

6.5 Strengths and limitations of the study (I-IV)

In large RCTs, the efficacy of treatments is evaluated in the ideal setting of selected patients. The strength of all our studies is that we assessed the effectiveness of treatments in routine circumstances in unselected patients.

All the patients in the present studies (I-IV) were gathered from the Helsinki University Central Hospital and from the Lappeenranta Central Hospital (II). Because patients with more severe diseases are treated in central or university hospitals, results cannot be generalized to all patients with the same diseases. However, because patients with severe diseases that need to be treated with biologicals are mostly directed to central hospitals, our data therefore most likely reflect the routine care setting in the treatment of arthritis patients with biologicals (II-IV).

A limitation in Study I was a low level of response to the first questionnaire (57%) and a high number of drop-outs (23%) on follow-up.

In Study III, costs were compared in a setting of one year before and one year during treatment with infliximab without any concurrent comparison group. In addition, that not all relevant costs are included in the analyses can be considered a weakness of that study.

In all our studies, the number of patients as a whole (II-IV) or in diagnostic groups (I) was small; this can also be considered a limitation.

SUMMARY AND CONCLUSIONS

In conclusion, effective treatment either with combinations of DMARDs or with TNF-inhibitors improves both clinical parameters and the HRQoL of patients with RA, improving their long-term outcome. In the case of unresponsiveness to the first TNF-inhibitor, a switch to the next one is the routine practice. The clinical effectiveness of switching has been demonstrated in small observational studies, and the same result was observed here. Furthermore, we could demonstrate that patients who have responded well to infliximab could be switched to etanercept without losing their drug response. Such a switch can prove useful in situations in which a patient is unable or unwilling to come to the hospital for infliximab infusions.

We also have shown that the one-year treatment with infliximab in routine practice saves neither medical nor work-disability costs. Further research should demonstrate whether any saving will be achieved in patients treated with biologicals in the earlier phase of the disease. These finding imply the necessity of developing a treatment for those RA patients who fail to respond to any TNF-inhibitors or to other biologicals.

We demonstrated the low HRQoL of patients with rheumatic diseases referred to the rheumatology clinic compared to that of the age-adjusted general population. HRQoL was lower not only in patients with chronic inflammatory joint diseases but also in patients with OA and arthralgia and fibromyalgia. The HRQoL improved significantly with conventional treatment in patients with RA and ReA. However, the current pharmacological treatment failed to improve the HRQoL of OA patients during the 8-month follow-up. Further research is necessary to assess the HRQoL of patients with differing diagnoses in routine care during longer periods of time.

Etanercept and adalimumab treatment had already improved significantly the HRQoL of our RA patients in the first 3 months. Despite the longstanding RA with its mean duration of 17 years, the improvement in HRQoL was significant. Another research implication would be to follow patients treated

with biologicals for longer periods to analyse whether the improvement of HRQoL will persist and how will it affect their long-term outcome.

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