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Disease activity, function and costs in early rheumatoid arthritis

the Swedish TIRA project

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ABSTRACT

Rheumatoid arthritis (RA) is a major cause of progressive joint damage and disability, and is associated with decline in quality of life, reduced ability to work and increased health care utilisation. The economic consequences of the disease are substantial for the individuals and their families and for the society as a whole. This thesis describes a 5-year follow up of 320 patients with early RA, enrolled between January 1996 and April 1998 in the Swedish multi-centre inception cohort TIRA (early interventions in rheumatoid arthritis). Health status, function and costs were investigated. Predictors of high costs were calculated, and an algorithm was constructed to predict future need for TNF-inhibitor treatment in patients not responding to traditional disease-modifying antirheumatic drugs (DMARDs).

Clinical and laboratory data, measures of functional capacity and self-reported assessments were collected regularly. In addition, patients completed biannual/annual questionnaires concerning all health care utilisation and days lost from work due to the disease. Within 3 months, improvements were seen regarding all variables assessing disease activity and functional ability, but 15% of the patients had sustained high or moderate disease activity throughout the study period. The scores of 'health assessment questionnaire' (HAQ) were similar for men and women at baseline, but had a less favourable course in women, who also had DMARDs more frequently prescribed.

Ambulatory care accounted for 76% of the direct costs during the first year. Women had more ambulatory care visits and higher usage of complementary medicine compared to men. Men ≥65 years had low costs compared to younger men and compared to women of all ages. In multiple logistic regression tests, HAQ, high levels of IgM-class rheumatoid factor (RF), and poor hand function increased the odds of incurring high direct costs. Poor hand function and pain increased the odds of incurring high indirect costs. Indirect costs exceeded direct costs all three years. The average direct costs were €3,704 (US$ 3,297) year 1 and €2,652 (US$ 2,360) year 3. All costs decreased over the years, except those for medication and surgery. The indirect costs were €8,871 (US$ 7,895) year 1 and remained essentially unchanged, similarly for both sexes. More than 50% were on sick leave or early retirement at inclusion. Sick leave decreased but was offset by increase in early retirement. 14 patients (5%) were prescribed TNF-inhibitors at the 3-year follow up, thus increasing drug costs substantially. However, they incurred higher costs even before prescription of anti-TNF therapy. At the 5-year follow-up (2001-2003), 31 patients (12%) were prescribed TNF-inhibitors. Baseline values of erythrocyte

sedimentation rate, C-reactive protein, anti-CCP antibodies and morning stiffness were significantly higher in this group. These patients were also to a larger extent RF-positive and carriers of the 'shared epitope' (SE). Anti-TNF treated patients were significantly younger and more often women. For men, a predictive model was constructed using baseline data including SE+ and IgA-RF >100 U/L and anti-CCP >240 U/L yielding a specificity of 98% and a sensitivity of 71%. For women, disease activity score (DAS28) at the 3-month follow-up proved to be a better predictor, and the final model comprised SE+ and 3-month DAS28>5.2, giving a specificity of 95% and a sensitivity of 59%.

ABBREVIATIONS

ACR	American College of Rheumatology
Anti-CCP	anti-cyclic citrullinated peptide
ACPA	antibodies against citrullinated peptides/proteins
ARA	American Rheumatism Association
CAM	complementary medicine
CI	confidence interval
CRP	C-reactive protein
DAS28	28-joint count disease activity score
DMARD	disease-modifying antirheumatic drug
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FCA	friction cost approach
HAQ	Stanford Health Assessment Questionnaire
HCA	human capital approach
HLA	human leukocyte antigen
ICF	International Classification of Functioning, Disability, and Health
Ig	immunoglobulin
MCP	metacarpophalangeal (joint)
MTP	metatarsophalangeal (joint)
NSAID	non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures for Arthritis Clinical Trials
OR	odds ratio
OT	occupational therapist
PIP	proximal interphalangeal (joint)
PGA	physician's global assessment of disease activity
PT	physiotherapist
RA	rheumatoid arthritis
RF	rheumatoid factor
ROC	receiver operating curve
SD	standard deviation
SE	shared epitope
SEK	Swedish kronor
SEM	standard error of the mean
SOFI	Signals of Functional Impairment
TIRA	Swedish acronym for 'early intervention in RA'
TNF	tumor necrosis factor
VAS	visual analogue scale
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I-IV).

I. Hallert E, Thyberg I, Hass U, Skargren E, Skogh T. Comparison between women and men with recent onset rheumatoid arthritis of disease activity and functional ability over two years (the TIRA project). Ann Rheum Dis 2003; 62: 667-670.

II. Hallert E, Husberg M, Jonsson D, Skogh T. Rheumatoid arthritis is already expensive during the first year of the disease (the Swedish TIRA Project). Rheumatology 2004; 43: 1374-1382.

III. Hallert E, Husberg M, Skogh T. Costs and course of disease and function in early rheumatoid arthritis: a 3-year follow-up (the Swedish TIRA project). Rheumatology 2006 45: 325-331.

IV. Hallert E, Husberg M, Persson J, Skogh T. Early predictors of TNF-targeted therapy in women and men with recent onset rheumatoid arthritis (the Swedish TIRA Project). (submitted)

INTRODUCTION

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease associated with tissue destruction, disability and pain (Scott et al. 2005). The course of the disease is progressive and imposes a considerable economic burden for the patients, their families and for the society (Kobelt et al. 1999, March and Lapsley 2001).

In 1958, the American Rheumatism Association (ARA), nowadays called American College of Rheumatology (ACR), suggested diagnostic criteria defining definite, possible, probable, and classical RA (Ropes et al. 1958). In 1987 the criteria were revised and intended for classification purposes rather than diagnostic criteria (Arnett et al. 1988) (Table 1).

***Table 1**. The 1987 revised ACR criteria for classification of RA. According to these, a patient can be classified as having RA if at least four criteria are satisfied.*

Criteria
1. Morning stiffness of ≥ 60 minutes*
2. Arthritis in three or more joint areas*
3. Arthritis in hand joints (wrist, MCP, PIP)*
4. Symmetrical arthritis (wrists, MCPs, PIPs, MTPs)*
5. Rheumatoid nodules
6. Positive rheumatoid factor test
7. Typical X-ray findings in hand- or wrist joints

* criterion 1 - 4 must have been present for at least 6 weeks.

The 1987 revised ACR classification criteria, which are still used as the golden standard, were based on patients with established disease and are rather insensitive in patients with very early disease. In RA-patients with very early arthritis (< 3 months), only 52% fulfilled 4 or more criteria (Machold et al. 2002). New tests for antibodies against citrullinated peptides/proteins (ACPA) have shown extremely high diagnostic specificity for RA and, apart from being as sensitive as rheumatoid factor (RF), the new generation of tests for antibodies to cyclic citrullinated peptides (anti-CCP) enable early diagnosis of RA

with high accuracy (Söderlin et al. 2004, Avouac et al. 2006). ACPA has also been shown to predict the development of future RA, especially in the presence of SE, and to predict an aggressive disease course and poor outcome regarding erosions and function (Forslind et al. 2004, Kastbom et al. 2004, Rönnelid et al. 2005, Nell et al. 2005, Berglin et al. 2006). Analysis of ACPA is likely to be included in future criteria for the classification/diagnosis of RA (Avouac et al. 2006). In order to allow comparison of results in future studies with historic references using the 1987 ACR criteria, however, RF must remain an important diagnostic test for many years to come (Skogh 2005).

The prevalence of RA in Scandinavia is 0.5-0.7%, with women being more often affected than men (Larsson et al. 1991, Simonsson et al. 1999). The annual incidence in Sweden has recently been calculated to 24/100 000, 29/100 000 for women and 18/100 000 for men (Söderlin et al. 2002). The prevalence increases with age and the peak age of onset is lower in women than in men. Although RA is more common in women than in men in all age groups, the gender difference is most obvious at younger age (Masi 1998).

The aetiology of the disease is unknown, but genetic as well as environmental factors and life style are of importance (Klareskog et al. 2004, Oliver and Silman 2006). Being a current or previous smoker is a risk factor for RF-positive RA and the risk increases with the cumulative dose (Stolt et al. 2003, Reckner Olsson et al. 2004). A clear cut gene-environment interaction has been shown regarding cigarette smoking and carriage of HLA-DRB1 gene alleles coding for the 'shared epitope' (SE) in anti-CCP-positive RA (Klareskog et al. 2006).

The course of the disease varies, but most patients develop a chronic progressive disease leading to pain, joint destruction and disability (Pincus et al. 1984, Rasker et al. 1987, Wolfe and Cathey 1991, Isomäki 1992, Möttönen et al. 1996, Scott et al. 2003). Life expectancy is reduced, mainly due to cardiovascular mortality (Wolfe et al. 1994, Goodson et al. 2005). Erosions develop early and within 3 years, 70% of the patients have developed erosive joint damage (van der Heijde 1995). The inflammatory process leads to pain, fatigue, restricted range of movement of joints and decreased muscle strength (Ekdahl and Broman 1992, Eberhardt and Fex 1995). After starting treatment, clinical measures of disease activity and functional ability improve substantially. However, although the inflammatory activity improves and the disease arrives at a stable state, joint damage and functional ability deteriorates (Pincus et al. 1984, Fex et al. 1996, Drossaers-Bakker et al. 1999, Welsing et al. 2001, Wick et al. 2004). Barrett et al reported that 33% of RA-patients had become permanently work

disabled within 2 years of disease (Barrett et al. 2000). The British early RA study (ERAS) reported that 17 % of the patients had undergone surgery during the first 5 years (Young et al. 2000) and in a Swedish early arthritis study, 17% of the patients had major joint replacement surgery performed during the first 10 years (Lindqvist et al. 2002).

Assessments

Disease activity

Many aspects must be considered when evaluating the disease in patients with RA. In order to standardize clinical trials, a consensus was presented in 1999 by "Outcome Measures for Arthritis Clinical Trials" (OMERACT), proposing that 5 domains should be covered in longitudinal observational studies, namely health status, disease process, organ damage, drug toxicity/adverse reactions, and mortality. In addition, 2 further domains, work disability and costs should be considered (Wolfe et al. 1999).

The World Health Organization's International Classification of Functioning, Disability and Health (ICF, WHO 2001) provides a comprehensive framework in order to evaluate the total impact of the disease (Stucki and Cieza 2004). The ICF is divided into 2 parts: (1) Functioning and disability, consisting of body function and structures and activities, and (2) participation and contextual factors, comprising environmental factors and personal factors (Figure 1). The structure demonstrates that health status can be measured at different levels, impairment, activity limitation and participation restrictions and shows how they interact. It can also be used to identify which domains are covered by a specific instrument and if other measures are needed to complete the investigation. ICF defines what should be measured, but not which measures that should be used.

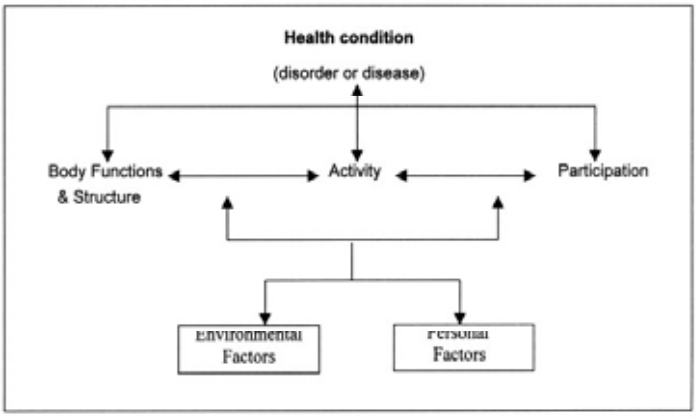


Figure 1. *International Classification of Functioning, Disability, and Health (ICF) (WHO 2001).*

Disease activity can be evaluated by tender and swollen joint count using a 28-count index (Prevoo et al. 1995), and acute-phase reactants such as serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Global assessment of disease activity can be assessed by the patient and by the physician on a visual analogue scale (VAS) and the disease activity score (DAS28) can be calculated comprising weighted values for tender and swollen joints, ESR and the patient´s global assessment. (Prevoo et al.1995). Several DAS algorithms exist and it has been described that ESR may be replaced by CRP (Skogh et al. 2003, www.das-score.nl 2003). Patient's estimation of early morning stiffness can also be used as a marker of disease severity. These measures represent impairments in body functions and structure in the ICF.

Function

Functional status can be assessed by questionnaires evaluating physical function, pain, general well-being and quality of life as judged by the patients. Self-reported data have proved to be as informative as other clinical and laboratory measures (Pincus et al. 2003). The most widely used instrument to assess functional status, is the Stanford Health Assessment Questionnaire (HAQ) (Fries et al. 1980). HAQ has been translated into many languages including Swedish, and the Swedish version of HAQ has been found to give valid information about the disease and functional ability (Ekdahl et al. 1988). Assessment of functional ability reflects a combination of structural damage and disease activity. HAQ correlates to disease activity at baseline and is

also a powerful predictor of future functional status (Sherrer et al. 1986, Eberhardt et al. 1990, Wolfe and Cathey 1991, Leigh and Fries 1992, Zeben et al. 1993, van der Heide et al. 1995, Singh et al. 1996, Harrison et al. 1996, Young et al. 2000, Uhlig et al. 2000, Jansen et al. 2000, Combe et al. 2003). Presence of rheumatoid factor, increasing age and female gender has also been associated with poor outcome (Sherrer et al. 1986, van der Heijde et al. 1992, von Zeben et al. 1993, Eberhardt and Fex 1995, Wiles et al. 2000, Scott et al. 2000b, Young et al. 2000, Kuiper et al. 2001). HAQ-scores have been reported to increase with disease duration by 0.031/year (Scott et al. 2000a). At baseline, most patients have considerable disability and HAQ is formed like a 'J-shaped' curve, showing initial improvement followed by a slow deterioration (Welsing et al. 2001, Scott et al. 2003, Pollard et al. 2005). In early disease, HAQ is influenced by pain and inflammatory activity and later on by structural joint damage (Guillemin et al. 1992, Scott et al. 2000a, Welsing et al. 2001). In the framework of the ICF, HAQ is referred to as a measure of activity limitation (Wolfe 2000).

Besides self-registered function, muscular strength and functional capacity can be measured by tests such as Signals of Functional Impairment (SOFI) (Eberhardt et al. 1988), walking speed and grip strength. Health status can also be assessed by generic instruments such as Euro-QoL (EQ-5D) and the Medical Outcome Survey Short Form (SF 36) (Ware and Sherbourne 1992), which are being increasingly used for RA patients (Lapsley et al. 2002, Ödegård et al. 2005, Thyberg et al. 2005). Disease-specific instruments have the advantage of being more sensitive to change, whereas generic instruments can compare health status in patients with different diseases.

Economic burden

General

The economic consequences of RA are substantial for the individual and their families and for the society (Pugner et al. 2000, Wong et al. 2001, Merkesdal et al. 2001, Lapsley et al. 2002, Kvien 2004, Rat and Boissier 2004). Health care costs are 2-3 times the costs for individuals of similar age and gender and increases with age and disease duration (Meenan et al. 1987, Jonsson et al. 1992, Gabriel et al. 1997a, Yelin and Wanke 1999). Work disability is however the most expensive consequence of RA and these costs exceed treatment costs in most studies (Meenan et al. 1987, Lubeck 1995, McIntosh 1996, Kobelt et al. 1999, Newhall-Perry et al. 2000, Jonsson and Husberg

2000, Leardini et al. 2002, Cooper et al. 2002, Ruof et al. 2003). As reviewed by Verstappen et al, the percentage of work disability differs between countries, due to different welfare facilities, but all studies show substantially increased risk of work disability versus the general population (Verstappen et al. 2004a). In Sweden, the total costs of RA in 1994 were estimated to almost 3 billion Swedish kronor (SEK) (€350 million) (Jonsson and Husberg 2000). In view of the new and very expensive biological agents, there is a growing need for economic evaluation included in clinical trials (Kalden 2002, Kavanaugh 2006). Drug costs are increasing rapidly and there is no tendency of slow-down. In Sweden, etanercept (Enbrel®) is the most sold cytokine-targeted anti-rheumatic drug today in terms of sales price. The cost for infliximab (Remicade®) in Sweden is lower and comes second (http://www.apoteket.se). (Figure 2).

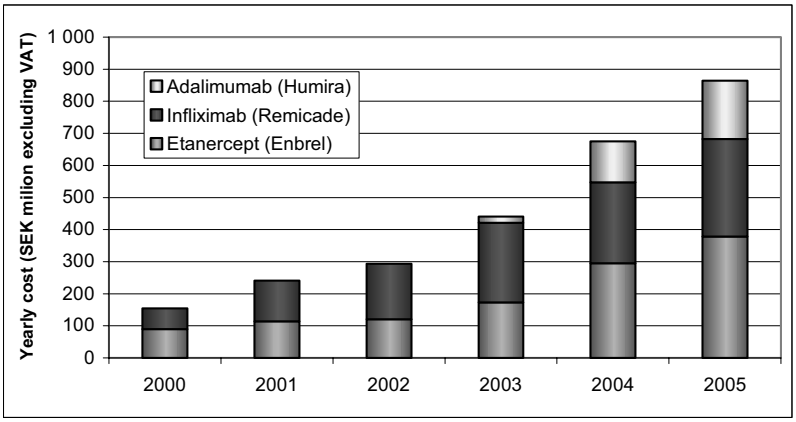


***Figure 2**. Sales price of TNF-inhibitors in Sweden years 2000-2005 (http://www.apoteket.se).*

Direct costs

In economic evaluations costs are generally divided into three components; direct costs, indirect costs and intangible costs. Direct costs refer to health care costs for which payments are made, such as:

- ambulatory care visits to physician, physiotherapist, occupational therapist and nurse
- drugs, hospitalisation, surgery and complementary care
- transportation costs, assistive devices, accommodations at home and home carers

In previous studies, costs for hospitalisation and surgical interventions have made up for the largest component of direct costs, reflecting that hospitalisations were more commonplace (Liang et al. 1984, Lubeck et al.1986, Yelin et al. 1996, McIntosh 1996, Clarke et al.1997, Gabriel et al. 1997a, Kobelt et al. 1999, Yelin and Wanke 1999). In recent years more patients are treated outside hospital, thereby shifting costs from inpatient care to outpatient care.

Indirect costs

Indirect costs are represented by loss of productivity due to sick leave or early retirement. This is of utmost importance in RA, since the ability to work is strongly associated to functional ability (Gabriel et al. 1997b, Kavanaugh et al. 2004). Different approaches can be made when calculating indirect costs. The most commonly used method is the human capital approach, which values the productivity of the individual as the gross income together with employer's contribution, estimating the value of lost productivity during the entire time of absenteeism. The human capital approach assumes full productivity and may favour persons with higher salaries, thus being more 'cost-effective' for expensive treatments, and giving no value to house-wives, students and retirees with no salary. Another approach is the friction method which assumes that the loss of productivity proceeds until the person returns to work or is replaced by someone unemployed, given that no society achieves full employment. This 'friction period' depends on the time it takes for the organisation to restore the original level of production and is usually considered to be 1-3 months, depending on the type of work and the time necessary for adaptation. Indirect costs calculated by the friction method yields accordingly lower costs compared to the human capital approach (Verstappen et al. 2005).

Intangible costs

Intangible or psychosocial costs represent pain, loss of function, limitations in leisure activities and reduced quality of life (Albers et al. 1999). These costs are considerable but rather difficult to quantify in economic terms and are usually omitted from health economy studies. They have, however, a large impact on the patient and his family and may very well be evaluated with other, more sensitive instruments.

Treatment

The optimal therapy involves modern drug treatment strategies together with interventions by a multiprofessional team to control the disease activity and to preserve function and prevent irreversible joint damage (Petersson 2005). The main goal is to achieve remission by controlling disease activity, thus maintaining functional capacity as well as working capacity and improving the quality of life. Early pharmacological treatment regimens and particularly, the new targeted biological agents inhibiting pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF), have been found to be highly effective in improving clinical status and functional ability, as well as halting radiographic progression (Lipsky et al. 2000, Emery 2002, Scott 2004, Breedveld et al. 2004).

The Swedish TIRA project

Sweden has a long tradition of population-based registers and several rheumatology registers have been established (van Vollenhoven & Askling 2005, Askling et al. 2006), e.g. the Lund register in 1985 followed by BARFOT in 1992, and the Swedish TIRA register 1996, all of which are early RA research registers. Subsequently several Swedish RA research registers have been established, e.g. EIRA dedicated to epidemiology, the two biologics registers SSATG and STURE, and the Northern Swedish RA register. The national Swedish RA register, which started as a quality assurance register in 1995, collects clinical data from all over Sweden and is associated with several Swedish RA research registers. Patient registers provide valuable databases for longitudinal observational studies real life situations. Data can be collected at regular follow-ups and describe long-term course of disease and identify predictors of outcome (van Vollenhoven and Askling 2005). Unusual side effects can easier be identified when regional registries are merged, thus increasing the area of coverage. Through linkages to national health and population registers, using the Swedish national registration numbers, valuable safety information can be gathered (Askling et al. 2006).

In 1996 a prospective study on recent onset RA ("TIRA") was started in cooperation between 10 rheumatology units in southeast Sweden and the Center for Medical Technology Assessment at Linköping University. TIRA is the Swedish acronym for 'early intervention in rheumatoid arthritis'. The main goal was to establish routines for obtaining an early diagnosis and rapid multiprofessional intervention. Further, the

TIRA project aimed at forming a research database for multidisciplinary research.

Three hundred and twenty patients were enrolled in the study and clinical and laboratory data were collected at inclusion, after 3, 6, 12, 18, and 24 months and then annually. Detailed questionnaires were completed regularly by the patients, reporting all health care utilisation and number of days lost from work due to the disease. At each visit the patient met a rheumatologist as well as a physiotherapist, occupational therapist and nurse. Besides medication, all patients were offered rehabilitation such as supervised dynamic exercises, pool training and hand training when necessary. The broad approach with multiprofessional interventions and extensive data registration at regular follow-ups during to date 8 years, makes this database quite unique. A comprehensive variety of aspects was investigated in this cohort of recent onset RA (Table 2).

Table 2. *The comprehensive data evaluated in the TIRA cohort*

- Demography, incl. socio-economic & psycho-social factors
- Exposure factors & lifestyle
- Genetic markers
- Disease markers
- Co-morbidity
- Disease activity (inflammation & tissue damage)
- Functional abilities & activity limitations
- Medication
- Quality of life
- Health economy

AIMS OF THE STUDY

The general aim of this thesis was to elucidate the course of the disease in a cohort of patients with recent onset RA, followed regularly in a longitudinal prospective study and to evaluate consequences of the disease.

Specific aims were:

- To describe and compare the disease course and consequences (disease activity; functional ability) for women and men in a 2-year perspective (paper I)

- To calculate costs during the first year after diagnosis and identify predictors of high direct and indirect costs (paper II)

- To calculate direct and indirect costs for men and women over 3 years and to shed light on costs and disease activity in a subgroup of patients who were prescribed TNF inhibitors (paper III).

- To pinpoint all patients prescribed TNF inhibitors during the 5-year follow-up. This was done to enable identification of a set of early laboratory and clinical markers identifying the patients not responding to traditional DMARDs and therefore ultimately selected for TNF targeted therapy (paper IV).

PATIENTS AND METHODS

All studies in this thesis are based on patients included in the TIRA cohort. In total, 320 patients, 215 women and 105 men, with recent-onset (onset of joint swelling ≤12 months) RA were enrolled from January 1996 through April 1998 from 10 rheumatology units in southeast Sweden corresponding to a catchment area of 1 million inhabitants. All primary health care units in the surroundings were requested to promptly refer all patients reporting swollen joints since at least 6 weeks, but not longer than 1 year, to the rheumatology unit at their connecting hospital. To be included in the Swedish TIRA project, the patients should be aged 18 or more and fulfil at least 4 of 7 criteria according to the 1987 revised ACR criteria (Arnett et al. 1988) *or* to suffer from morning stiffness (60 minutes or more as judged by the patients), symmetrical arthritis and arthritis in small joints (metacarpophalangeal / proximal interphalangeal / metatarso-phalangeal joints or wrists). The mean age (standard deviation, SD) of the patients at inclusion was 56.2 (SD 15). Women were younger, (54.7, SD 15) than were men (59.1, SD 15).

Clinical and laboratory data were collected at inclusion and after 3, 6, 12, 18, 24 months and then once a year. At each visit the patient met a rheumatologist as well as a physiotherapist, occupational therapist, and nurse, and was offered medication and multiprofessional interventions when judged necessary.

Whole blood was available from 181 patients (mean age 57.5 years, 71% women). DNA was prepared from these samples and typed regarding SE at the national forensic genetics department in Linköping. SE is a gene product from the 'human leukocyte antigen' (HLA) DRB-1 locus and defined here as HLA-DRB1*01, *0401, *0405, *0408, *0409, *0410, *0413, *0416, *0419, *0421, or *10.

At the 1-year follow-up, 297 patients remained in the study. After 2 and 3 years, the numbers were 284 and 276 respectively. After the 3-year follow-up, 2 participating units withdrew from the study. For the purpose of paper IV, all patients from the 2 missing units were checked up. Thus, 266 patients (185 women and 81 men) were evaluated in order to identify patients who had been prescribed TNF-inhibitors some time during the first 5 years after diagnosis. Fifty-four patients dropped out during the period. Ten patients died, 6 moved from the area and 38 did not wish to participate further for various reasons. The dropouts were significantly older compared to the study

group (65 vs 54 years), walked slower and had a lower average grip force. The average level of anti-CCP antibodies was lower among the dropouts compared to the study group (246 U/L vs 435 U/L). All other variables were similar in the two groups. The number of patients at different follow-ups is shown in Table 3.

Table 3. *The number of patients at different follow-ups.*

	Inclusion	Year 1	Year 2	Year 3	Year 4	Year 5
Patients in the TIRA study	320	297	284	276	195	179/266
Patients with health care data	303	211/276	254	187/195		

All patients gave written informed consent to participate. The study protocol was approved by the local ethics committees associated with the participating hospitals.

Disease and disease activity

Particle-agglutinating rheumatoid factor was analysed at inclusion, and erythrocyte sedimentation rate and serum C-reactive protein (CRP) were analysed at all visits. These analyses were performed on a routine basis at the local hospital laboratories. Sera frozen after the inclusion visit were analysed at the research laboratory in Linköping regarding IgM- and IgA-RFs (Autozyme™ RF IgM and IgA respectively, Cambridge Life Sciences, Cambridge, UK) and anti-CCP antibodies (Immunoscan RA CCP2, Eurodiagnostica, Arnhem, the Netherlands). The cut-off limits for positive IgM- and IgA-RF (34 and 15 Units/mL respectively) were based upon the 95th percentile in 100 healthy blood donors. The cut-off limit for anti-CCP antibodies was set at 25 units/mL as suggested by the manufacturer (at this level none of 80 sera from healthy blood donors turned out positive).

The number of swollen and tender joints was registered on a 28-joint score (Prevoo et al. 1995). The average duration of morning stiffness for the last week was estimated by the patient. The physician's global assessment of disease activity (PGA) was scored 0-4, (0 = no activity, 1 = low activity, 2 = moderate activity, 3= high activity, 4 = very high

activity). Disease activity was also assessed by calculating the 28-joint count disease activity score (DAS28) (Prevoo et al. 1995).

Function and general health

Tests of physical function were performed using a simple range-of-movement index designated 'signs of functional impairment' (SOFI) comprising 3 parts; assessment of hand function, upper limb function and lower limb function (Eberhardt et al. 1988). Each test has a score 0-2, where 0 corresponds to normal function, 1= slight disability and 2= severe disability. The scores are added up and the total range is 0-16 for hands, 0-12 for upper limbs and 0-16 for lower limbs, higher scores indicating increasing disability. Walking speed was measured by asking the patient to walk 20 metres as fast as possible. The Swedish version of the Health Assessment Questionnaire (HAQ) (Fries et al. 1980, Ekdahl et al. 1988) was used. Grip force was measured with an electronic device (Grippit, AB Detektor, Göteborg, Sweden). The average grip force during 10 seconds for the right hand was recorded (Nordenskiöld and Grimby 1993). The patients were also asked how much pain they had felt on average during the last week. This was estimated on a 100-mm visual analogue scale (VAS) ranging from 0 (no pain at all) to 100 (worst possible pain). General health was estimated in the same manner, 0 representing 'best possible well-being' and 100 'worst possible well-being'.

Ongoing, instituted, and withdrawn medication with disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and analgesics were registered at all visits. An overview of the assessments in the TIRA study is shown in table 4.

Table 4. *Overview of the assessments in the TIRA study.*

Disease • anti-CCP • RF (agglutinating; IgA-/IgM-) • co-morbidity • genetic markers **Intervention** • medication • physiotherapy / occupational therapy **Tissue damage** • COMP • radiographs	**Disease activity** • swollen joint count • tender joint count • general health (VAS) • ESR *DAS28* • CRP • morning stiffness • pain (VAS) • physicians global assessment	**Function** • HAQ • SOFI 1-2-3 • walking • grip strength **Health economy** • health care utilisation • sick-leave • EQ-5D **Health-related quality of life** • SF-36

Health care questionnaire

Baseline demographic data including age, marital status, working status and educational level were collected at enrolment. In addition, all patients were provided with a detailed questionnaire to be filled out during the following 6 months, reporting all health care utilisation and days lost from work during the period. At the 6-month follow up, the questionnaire was collected and a new one was distributed to be completed over the next 6 months. During the first 2 years, questionnaires were provided biannually, and once a year during the following years.

All visits to health professionals were reported as well as admissions to hospital, surgical procedures, and all drugs (prescribed and over the counter) and their dosages. The usage of complementary medicine was also reported. All days lost from work due to illness and rehabilitation were reported as well as early retirement due to permanent work disability. Data from the semi-annual questionnaires were put together and reported yearly. Information about work absenteeism was summed up and presented as total number of days lost from work per year, part-time sickness leave being recalculated to full-time sickness leave. The cost of one month's full-time work was calculated using an average of the gross income of all gainfully employed Swedish full-time workers, corresponding to 30,000 SEK (€ 3,243) (including taxes, social insurance and other fees). Costs were calculated using a human

capital approach in patients 18-65 years, who were unable to work due to the disease. The cost of hospitalisation was based on an average per diem cost in a medicine ward, and all admissions due to surgical interventions were valued according to the NordDRG system (Serden et al. 2003). Unit costs were rated using tariffs from the Swedish Federation of County Councils (Landstingsförbundet Stockholm) and the cooperation in the Southeast of Sweden Medical Services Region (www.lio.se/templates/Page.aspx?id=13332). Costs were calculated from a societal perspective comprising both direct and indirect costs, regardless of payer. Unit costs for used resources are presented in Table 5.

Table 5. *Unit costs for each resource use. Values are in Swedish kronor (SEK) and euro (€) at 2001 prices.*

Resource	Unit cost (SEK)	Unit cost (€)
physician visit	2 100	227
nurse visit	700	76
physiotherapist visit	700	76
occupational therapist visit	700	76
hospitalisation / day	2 800	302
total joint replacement hip/knee	76 862	8 309
foot surgery	33 151	3 584
major hand surgery	19 141	2 069
minor hand surgery	12 365	1 337

€ 1 = SEK 9.25

Statistical analyses

Demographic and clinical characteristics were expressed as mean with standard deviation (SD) or median and range. Comparisons between groups were tested by Student's t- test or Wilcoxon's signed rank test for paired samples and Student's t-test or Mann-Whitney U-test for unpaired samples. Chi-square test or Fisher's exact test were used to test differences in proportions. Costs were presented as mean (SD) in Swedish kronor (SEK), euro (€) and US dollars (US$) and were adjusted to 2001 values, using the consumer price index (**papers I, II and III**).

The patients were divided into two groups in order to find predictors for high costs. A cut-off point for direct costs was set at 34 000 SEK / year (€ 3 675), defining 1/3 of the patients as the high direct cost group and 2/3 as the low direct cost group. Indirect costs were calculated for patients with no indirect costs and for patients with indirect costs. Stepwise multivariate logistic regression tests were performed with high costs as dependent variable. Variables associated to high costs with p-value <0.2 were selected from the univariate analysis and entered into regression models. Associations with the independent variable were presented as odds ratios (OR) with 95% confidence intervals (95% CI) indicating the likelihood that patients with predictive variables will incur high costs (**paper II**).

For the purpose of evaluating if an early set of laboratory and clinical markers could identify the patients, who were later prescribed TNF inhibitors, cut-off values were deduced for continuous data from receiver operating characteristics (ROC) curves and the area under the curve (AUC) was computed, providing a measure of the discriminative ability. Different combinations of laboratory data and clinical data were performed to discriminate between patients receiving and those not receiving TNF-inhibitor treatment ('TNF group' and 'non-TNF group' respectively), aiming at maximizing the specificity without losing sensitivity. The positive predictive value (PPV) and the negative predictive value (NPV) were also calculated (Figure 3) (**paper IV**).

	TNF group	non-TNF group		
positive test	A	B	**PPV**	A/(A+B)
negative test	C	D	**NPV**	D/(C+D)
	sensitivity A/(A+C)	**specificity** D/(B+D)		

Figure 3. *Calculations of sensitivity and specificity together with the positive predictive value (PPV) and the negative predictive value (NPV).*

All tests were 2-tailed and p<0.05 was considered to be statistically significant. The statistical calculations were performed using SPSS 11.5 and 14.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

Course of disease and function (papers I and III)

At inclusion most patients were substantially affected by the disease. The mean HAQ score was 0.9 (SD 0.6; range 0 - 3) and DAS28 was 5.3 (SD 1; range 1.5 - 8.2). Men were older and had a higher average count of swollen joints compared to women. They were also more affected regarding function in hands and upper limbs. Otherwise, no gender differences were recorded.

The patients were assessed at regular follow-up visits and highly significant improvements were seen for all variables within the first three months. Disease activity then remained unchanged. Function variables followed the same pattern during the first year, but tended to worsen over the years. HAQ scores were similar for men and women at baseline, but had a much less favourable course in women at all follow-ups (Figure 4).

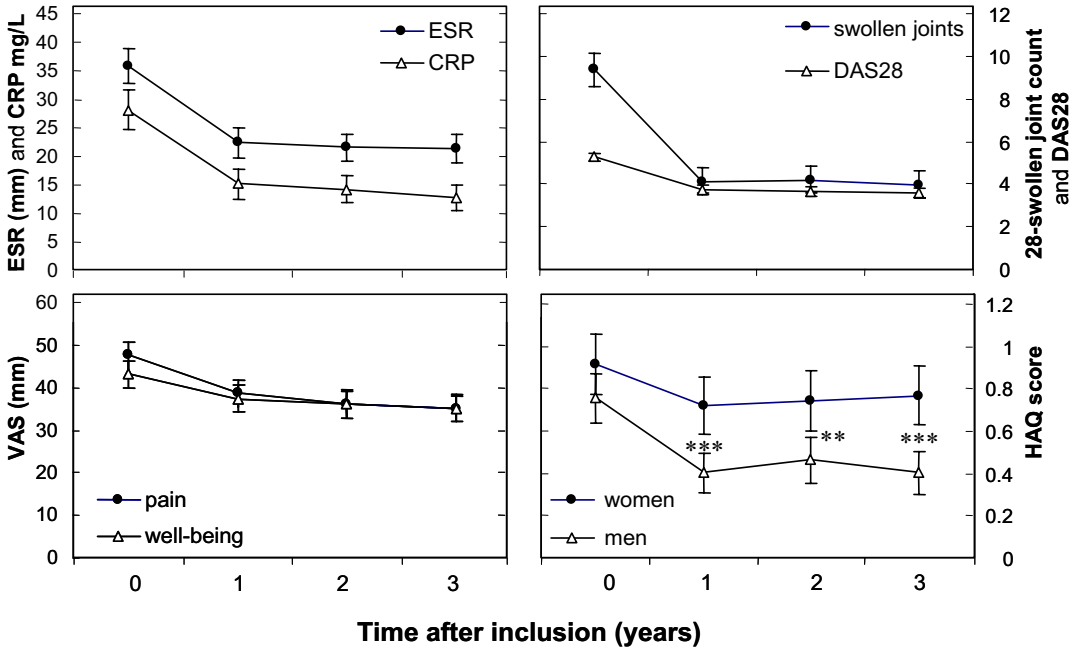


Figure 4. Clinical *and laboratory data (mean with 95%CI) for the total group during the first 3 years and HAQ-scores for men and women respectively. ** represents p=0.002 and *** p<0.0001*

Despite the intention to institute DMARDs rapidly, only about 60% took such drugs three months after the diagnosis of RA. The prescription of drugs differed somewhat between men and women during the second year and at the 2-year follow-up, DMARDs were prescribed to 71.4% of the women compared to 56.4% of the men (p<0.001) (Table 6).

Table 6. *Proportions of prescribed drugs for men and women (%) and p-value for difference between men and women.*

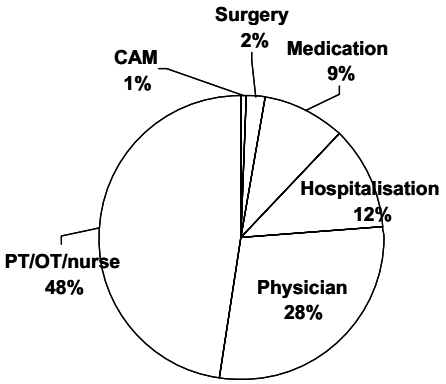
		DMARDs	NSAIDs	analgesics	oral corticosteroids	p-value
Month 0	women	2.5	71.0	26.5	19.2	
	men	2.2	75.9	25.2	20.6	
Month 3	women	61.5	61.8	26.3	39.2	
	men	62.2	62.5	30.6	38.7	
Month 6	women	66.6	60.4	28.6	38.5	
	men	71.9	60.3	29.6	43.2	
Month 12	women	71.9	61.2	29.8	35.7	
	men	72.7	61.2	29.4	37.7	
Month 18	women	72.4	66.2	40.5*	34.7	
	men	62.5	55.4	27.7	38.5	
Month 24	women	71.4***	62.5	40.1	37.0	* p<0.05
	men	54.6	57.7	33.0	32.1	*** p<0.001

Costs and predictors of costs (paper II)

At the 1-year follow up, health care questionnaires were available in 211 cases (71%), 146 women and 65 men. There was no difference in baseline characteristics for responders and non-responders regarding demographic data, HAQ, DAS28, or laboratory data.

Direct costs

The average annual direct cost was SEK 35 694 (€ 3 858), range SEK 12 600 - 276 093 (€ 1 362 – € 29 843). The ambulatory care visits accounted for 76.1% of the direct costs, hospitalisation 11.6% and medication for 9.4%. Approximately 1/3 of the costs for health professionals were related to nurse visits and included drug toxicity monitoring (Figure 5).



PT/OT/nurse	17 013 SEK
Physician	10 161 SEK
Hospitalisation	4 140 SEK
Medication	3 347 SEK
Surgery	748 SEK
CAM	284 SEK

Figure 5. *The average cost per patient and year (SEK) and the distribution of direct costs during the first year (% of total direct costs).*
PT=physical therapist, OT=occupational therapist, CAM=complementary medicine

Women had significantly more visits to the physician compared to men and used more complementary medicine. They also had higher costs for hospitalisation than did men; 5 427 vs 1 249 SEK (€ 587 vs € 135) and underwent more surgery year 3.

Indirect costs

One hundred and forty-one patients were ≤65 years of age. At inclusion, 71 patients (50%) were working, 62 (44%) were on sick leave and 8 patients (6%) were already early retired. During the first year, there was a shift towards increased sick-leave and early retirement (Table 7).

Table 7. *Employment status for patients ≤65 years of age at inclusion and during the first year.*

	at inclusion patients n(%) n=141	*during* the first year patients n(%) n=141
working	71 (50%)	52 (36%)
on sick-leave	62 (44%)	74 (53%)*
early retired	8 (6%)	15 (11%)

* sick leave more than 30 days during the year

The average indirect cost per patient was 80 728 SEK (€ 8 726) during the first year, indirect costs thus accounting for almost 70% of the total costs.

Predictors of high direct costs

Costs were skewed with few patients incurring the highest costs. An arbitrary cut off level was set at 34 000 SEK / year (€3 675), defining 1/3 of the patients as the high direct cost group and 2/3 as the low direct cost group (Figure 6).

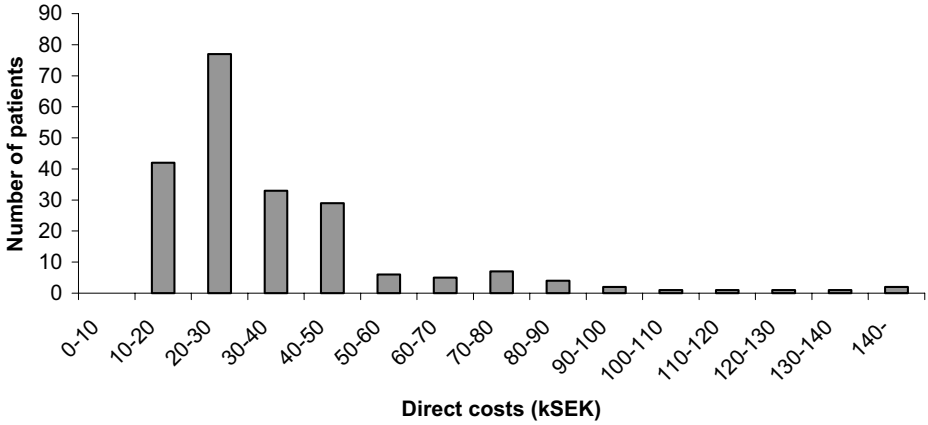


Figure 6. *Distribution of direct costs for all patients during the first year.*

A comparison of baseline data was done between the high-cost group consisting of 72 patients, 53 women and 19 men, and the low-cost group, consisting of 139 patients, 92 women and 47 men. Variables associated with high costs were entered in a forward stepwise regression model with high direct costs as dependent variable leaving HAQ as a significant predictor of high direct costs OR 3.3 (95% CI 1.6-6.8, p<0.001). IgM-RF and hand function (i.e. reduced range-of-motion in hands) were also included in the final model. IgM-RF gave OR 1.002 (95%CI 1.0-1.003, p=0.045) and hand function OR 1.177 (95%CI 1.0-1.37, p=0.033).

Predictors of high indirect costs

Fifty-two patients, 41 women and 11 men, had no indirect costs during the first year and they were compared to the remaining 89

patients, 63 women and 26 men, with costs (Figure 7). In the final regression model, poor hand function OR 1.338 (95%CI 1.1-1.6, p=0.002) and pain OR 1.017 (95%CI 1-1.03, p=0.035) at inclusion turned out as predictors of sick leave and early retirement during the first year.

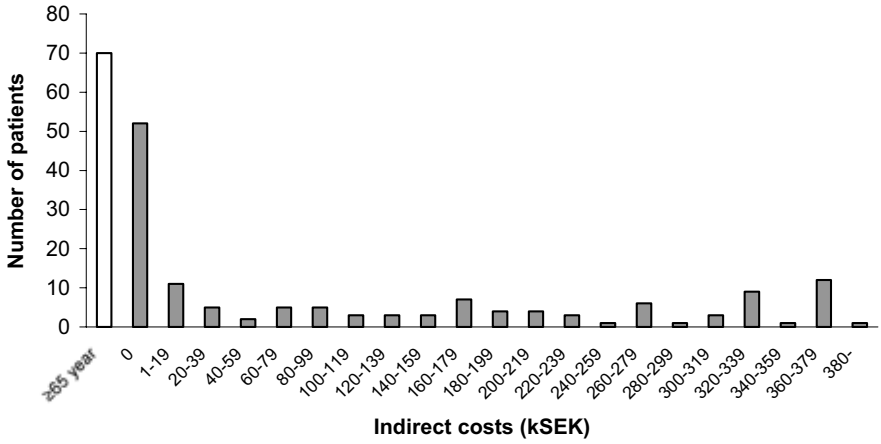


Figure 7. *Distribution of indirect costs for all patients during the first year.*

Costs over 3 years (paper III)

After the initial improvement, all measurements reflecting disease activity remained more or less stable over the following 3 years but function, as measured by walking velocity and SOFI range-of-movement tests, slowly deteriorated. Almost 25% of the patients went into remission (DAS28 <2.6) but approximately 15% had a sustained high or moderate disease activity during all 3 years (Figure 8).

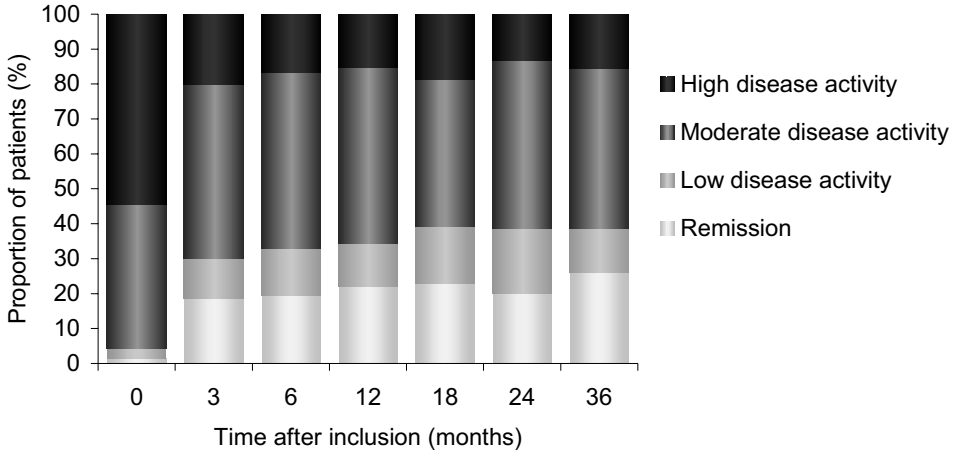


Figure 8. *Disease activity during the first 3 years. Remission corresponds to DAS28 <2.6, low disease activity to DAS28 2.6-3.1, moderate disease activity to DAS28 3.2-5.0, and high disease activity to DAS28 ≥5.1.*

Average annual direct costs per patient decreased from SEK 34 258 (€3 704) year 1 to SEK 24 592 (€2 652) year 3, while indirect costs were essentially unchanged; SEK 82 053 (€8 871) year 1 and SEK 81 738 (€8 837) year 3. Indirect costs exceeded direct costs by a factor 2.4 during the first year, by factor 2.9 the second year and factor 3.3 during the third year.

The costs for ambulatory visits decreased substantially from the first to the third year, SEK 26 500 vs SEK 13 050 ($p<0.0001$). Costs for hospitalisation also decreased, but on the contrary costs for drugs and surgical interventions increased. The increasing expenditures for drugs were entirely due to the introduction of the biological pharmacotherapy in the end of year 2.

During this period, 14 patients (5%) in the cohort were prescribed TNF-inhibitors and this affected the average drug costs substantially. The mean cost during the third year for the patients with TNF-inhibitors was SEK 70 800 (€7 654) compared to SEK 4 078 (€441) for patients without biological agents ($p<0.0001$). The drug costs as well as total direct and indirect costs were, however, higher for the future TNF-inhibitor group, even before the start of anti-TNF treatment, indicating that these patients were more affected by the disease than the others. In table 9, the costs for drugs are showed separately, but are also included in the total sum of direct costs (Table 8).

Table 8. *Costs (SEK) for patients prescribed TNF-blockers 2 years after enrolment compared to those who did not receive TNF-blockers.*

		anti-TNF	mean (SD)	median	p value
Year 1	drug costs	no	3 047 (3370)	2 281	
		yes	6 315 (6814)	3 116	**0.038**
Year 2	drug costs	no	3 932 (4609)	2 788	
		yes	12 448 (20339)	3 525	0.227
Year 3	drug costs	no	4 078 (7126)	2 229	
		yes	70 800 (49279)	101 849	**<0.0001**
Year 1	direct costs	no	32 994 (21895)	24 622	
		yes	62 056 (72268)	36 984	**0.034**
Year 2	direct costs	no	25 446 (21498)	19 843	
		yes	59 931 (66159)	32 663	**0.015**
Year 3	direct costs	no	20 679 (17526)	13 335	
		yes	104 097 (82019)	119 878	**<0.0001**
Year 1	indirect costs	no	77 125 (125583)	0	
		yes	190 479 (159718)	241 131	**0.011**
Year 2	indirect costs	no	74 881 (128156)	0	
		yes	161 822 (163728)	109 419	**0.018**
Year 3	indirect costs	no	75 307 (130912)	0	
		yes	214 652 (178796)	314 675	**0.016**

€1 = SEK 9.25 = US$ 0.89

The individual distribution of direct costs for patients in the TNF and non-TNF groups respectively, before and after the start of anti-TNF treatment is shown in Figure 10. The costs for surgery, hospitalisation, ambulatory care visits and drugs were higher for the TNF patients compared to the non-TNF during the first 2 years, and during year 3 the drug costs were much higher for TNF-patients as expected. The costs for surgery continued to be higher for patients in the TNF group, but ambulatory care visits decreased and costs for hospitalisation were zero (Figure 9).

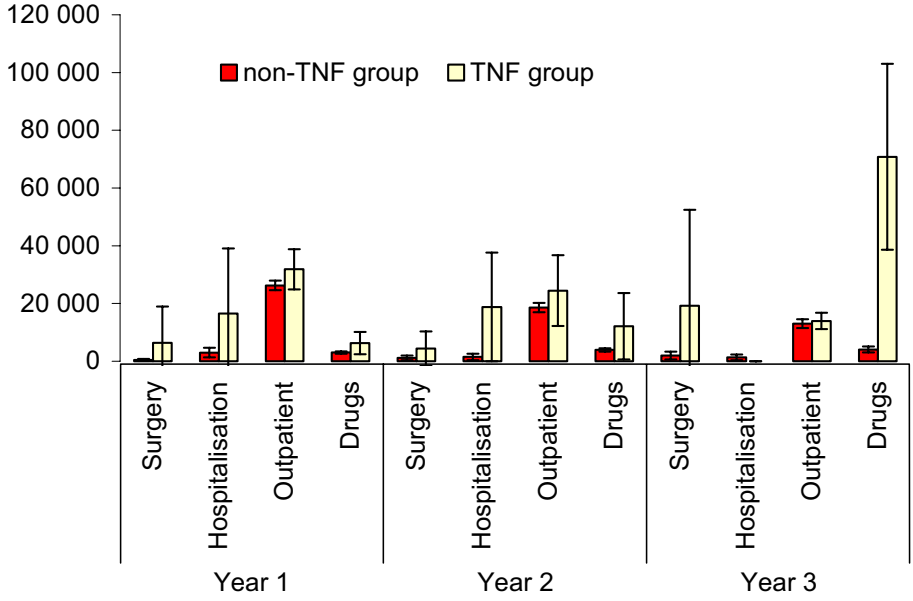


Figure 9. *The distribution of the direct costs (SEK) for patients prescribed and not prescribed TNF- blockers two years after enrolment (mean with 95%CI).*

The employment rate remained mainly unchanged during the first 3 years. At inclusion, younger patients were employed to a higher extent than older patients. Approximately 80% of the patients below 35 years of age were working, compared to 40% in the group ≥ 35 and this pattern persisted over time. In general, costs for sick leave decreased, but were offset by increasing costs for early retirement, due to permanent work disability.

Indirect costs were higher for those with low educational level. When controlling for age, however, the differences decreased somewhat since educational level was strongly dependent on age (Figure 10).

Figure 10. *Total indirect costs over 3 years for patients < 65 years of age according to age and educational level.*

There was no reduction of indirect costs for the patients treated with TNF-inhibitors. They were severely affected by the disease and most patients were already on long-term sick leave.

Early predictors of TNF-targeted therapy (paper IV)

At the 5-year follow-up, in total 31 patients (11.7%) were prescribed TNF-inhibitors. A higher proportion of women were given TNF-inhibitors compared to men, 23 women versus 8 men. Patients who were prescribed TNF-inhibitors were younger and had less co-morbidity than those in the non-TNF group. All patients except one in the TNF-group were anti-CCP positive and all except one were SE+. The mean levels of anti-CCP antibodies and IgA-RF were significantly higher in the TNF-patient group (p=0.002 and p=0.014 respectively). ESR was significantly higher in the TNF group (48 vs 34 mm) and there was a strong tendency for a higher baseline CRP in the TNF-group compared to the non-TNF patients (38 vs 27 mg/L). The measures of functional capacity did, however, not differ between the groups (Table 9).

Table 9. *Baseline characteristics for patients with and without TNF- blockers and p-value for difference between the groups. The TNF-group refers to patients who were prescribed TNF-blockers some time during the first 5 years. Data are mean (SD) or n (%).*

	no TNF n=235	TNF n=31	p
age	55 (14)	49 (14)	0.035
ACR-criteria (0-7)	4.5 (0.7)	4.6 (0.6)	ns
swollen joints(28)	9.3 (6)	10.6 (6)	ns
tender joints(28)	9 (7)	9.2(9)	ns
morning stiffness (min)	101 (65)	133 (80)	0.017
PGA (0-4)	2 (0.7)	2 (0.9)	ns
DAS-28	5.2 (1)	5.5 (1)	ns
comorbidity yes/no (%)	33	16	0.026
ESR (mm/h)	34 (23)	48 (26)	0.003
CRP (mg/L)	27 (26)	38 (34)	0.054
IgM-RF (0-720 U/L)	224 (227)	225 (215)	ns
IgA-RF (0-720 U/L)	85 (135)	121 (164)	ns
anti-CCP (12.5-1600 U/L)	395 (508)	755 (539)	0.002
IgM-RF+ n(%)	198 (74)	23 (91)	0.014
IgA-RF+ n(%)	200 (71)	24 (79)	ns
anti-CCP+ n(%)	186 (63)	23 (96)	0.002
IgM-RF+ IgA-RF+ anti-CCP+ n(%)*	182 (59)	22 (77)	ns
HLA-DRB1 shared epitope n(%)**	151 (71)	23 (96)	0.011
HAQ (0-3)	0.84 (0.5)	1 (0.5)	ns
wellbeing (mmVAS)	43 (25)	45 (25)	ns
pain (mm VAS)	48 (24)	50 (26)	ns
grip force (N)	119 (92)	102 (86)	ns
walking time (sec)	14 (6)	15 (7)	ns
hand function (0-16)	2.7 (2.6)	3.2 (3)	ns
upper limb (0-12)	1.2 (1.8)	0.8 (1.2)	ns
lower limb (0-16)	2.2 (2)	2 (1.9)	ns

* being positive for all 3 antibodies
** HLA-DRB1 corresponds to carriage of at least 1 allele
PGA=physician global assessment
IgM-RF was available in 221 patients, IgA in 224, anti-CCP in 209 and HLA-DRB1 in 174 patients

DAS28 at baseline was similar comparing the TNF-group and the patients that were not selected for TNF-blocker therapy during the first 5 years of the study. At the first clinical follow-up, 3 months after inclusion, the non-TNF-group had improved significantly, whereas the TNF-group had not. This difference remained highly significant until TNF-blockers were instituted after 2 years (Figure 11).

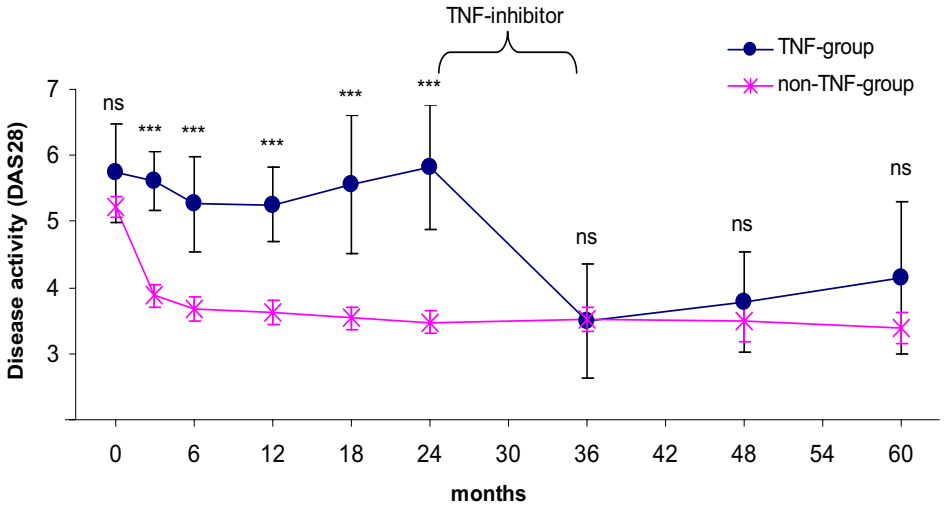


Figure 11. *DAS28 (mean values with 95%CI) during the first 5 years for TNF- patients who were prescribed TNF-inhibitors between month 24 and month 36 and non-TNF patients. P-value for difference between groups. *** = p<0.0001*

The number of swollen joints showed a similar pattern with no sustained response to treatment until anti-TNF treatment was started.

All patients were given conventional DMARD therapy prior to TNF prescription. In all cases except one, methotrexate had been used without sufficient effect (Table 10). On average, the patients received 2.7 DMARDs before TNF-inhibitor institution and treatment strategies were changed on average 2.7 times from the time of inclusion until TNF treatment was started. Twenty-one patients received combination therapy and 10 patients mono- therapy prior to TNF prescription. All patients except one starting TNF-inhibitor treatment were still on that medication at the 5-year follow-up. The patient who stopped treatment was severely disabled due to other diseases besides arthritis and did not wish to continue the TNF-inhibitor medication. Three patients switched between infliximab and etanercept due lack of efficiency and side effects.

***Table 10**. Prescription of DMARDs, numbers of combination therapies and numbers of different treatment strategies in 31 patients before starting TNF blocker therapy.*

pat	MTX	SLZ	CyA	HCQ	gold	PcA	CP	LEF	number of DMARDs	combi-nation therapy	no of combi-nations	no of treatment strategies	TNF change*
1	x		x				x		3	x	2	4	
2	x	x	x						3	x	1	2	
3	x	x							2	x	1	2	I->E
4	x								1			1	
5	x		x		x				3	x	2	3	
6	x								1			1	
7	x	x		x		x	x		5	x	2	4	
8	x			x					2	x	1	2	
9	x	x	x		x				4			3	E->I
10	x							x	2			2	
11	x	x	x	x	x				5	x	4	5	
12	x	x							2			2	
13	x	x	x						3	x	1	3	
14	x	x	x						3	x	1	2	E->I
15	x	x							2			2	
16	x	x	x						3	x	1	3	
17	x		x						2	x	1	2	
18	x			x	x				3	x	1	3	
19	x	x	x	x	x				5	x	3	6	
20	x		x			x			3	x	1	3	
21	x							x	2			2	
22	x		x		x	x			4	x	2	4	
23	x	x	x	x					4			4	
24				x					1			1	
25	x	x							2	x	1	2	
26	x	x	x						3	x	2	2	
27	x	x		x					3	x	1	3	
28	x								1			2	
29	x	x							2	x	1	2	
30	x	x							2	x	1	2	
31	x	x	x						3	x	2	4	
	30	18	15	8	no 6	3	2	2	mean 2.71	21		mean 2.68	

MTX=methothrexate SLZ=sulfasalazine CyA=cyclosporin-A HCQ=hydroxychloroquine
PcA=D-penicillamine CP=cyclophosphamide LEF=leflunomide
*I=infliximab E=etanercept

In order to distinguish future TNF-patients, not responding to traditional DMARD therapy, from non TNF-patients, different clinical and laboratory baseline data were evaluated. The presence of SE was

highly sensitive for TNF-patients, 94% for women and 100% for men. For continuous data, cut-off levels were deduced from receiver operating characteristics (ROC) curves, separately for both genders, providing a measure of the discriminative ability between patients receiving and not receiving TNF-blocker treatment.

In males all TNF-patients had a baseline level of anti-CCP above 240 U/L, giving a sensitivity of 100% and a specificity of 60% at that level. In females, the cut-off level of 240 gave a lower sensitivity (81%) but approximately the same specificity. At a cut-off level of 47, the sensitivity was 94% in females, but the specificity dropped to 44%. However, since SE and anti-CCP are highly associated, a high anti-CCP level did not add much information for women if SE was already in the model. Presence of SE and high levels of anti-CCP are thus rather interchangeable in the female group.

IgA-RF was useful only in the male group, with a cut-off level of 100U/L, giving a sensitivity of 75% and a specificity of 76%. IgM-RF had no discriminative ability. DAS28 was similar at baseline between groups, but the DAS-level at 3-month follow-up proved to be useful for women.

Since data were different for men and women, 2 models were calculated. For men, IgA-RF>100 alone gave a specificity of 76% and a sensitivity of 75%. Adding anti-CCP>240 increased the specificity to 89% without changing the sensitivity. In the final model, including the SE, the specificity was further increased to 98% and the sensitivity was 71%. For women, the final model included 3-month DAS28 >5.2 and SE. The DAS28 alone had 89% specificity and 57% sensitivity and adding SE to the model increased both specificity and sensitivity (Table 11).

***Table 11**. Specificities and sensitivities for SE and adapted cut off levels for RF, anti-CCP, DAS28 and combinations of data for men and women respectively.*

predictor	specificity %	sensitivity %	NPV %	PPV %
Female model				
HLA-DRB1 (SE)	35	94	97	19
DAS28>5.0*	85	65	94	39
DAS28>5.2	89	57	93	43
anti-CCP>47 U/L	44	94	98	17
anti-CCP>240 U/L	56	81	96	18
DAS28 >5.2 + anti-CCP>47 U/L	93	44	93	44
SE + DAS28 >5.2	95	59	93	67
Male model				
HLA-DRB1 (SE)	16	100	100	14
IgA-RF>100	76	75	95	32
anti-CCP>47 U/L	43	100	100	19
anti-CCP>240 U/L	60	100	100	25
anti-CCP>700 U/L	81	71	96	33
IgA-RF>100 + anti-CCP>240 U/L	89	75	96	50
SE + IgA-RF>100 + anti-CCP>240 U/L	98	71	96	83

* DAS-scores refer to DAS28 at the 3-month follow-up
NPV=negative predictive value
PPV=positive predictive value

DISCUSSION

Disease and function (papers I and III)

At inclusion, the patients had active arthritis with an average DAS28 of 5.3. Highly significant improvements were seen after 3 months and the measurements then remained stable over the following years. The disease variables were similar for men and women, but functional capacity as measured with HAQ had a much less favourable course in women (Table 12). Compared to men, women had DMARDs and analgesics more frequently prescribed and this might suggest that women had a more severe disease. Women also used more assistive devices (Thyberg et al. 2004). Several studies have concluded that women have a more active inflammatory and disabling disease compared to men and that they have lower remission rates (Thompson and Pegley 1991, Deighton et al. 1992, van der Heide et al. 1995, Katz and Criswell 1996, Smedstad et al. 1996, Pease et al. 1999, Young et al. 2000, Kuiper et al. 2001, Lapsley et al. 2002, Tengstrand et al. 2004). Weyand et al found, although erosive disease was more common in men, that the structural consequences of joint destruction were pronounced in women and led to more frequent joint surgery (Weyand et al. 1998). Forslind reported that men with RA had a higher rate of reduced bone mineral density (BMD), but that reduced BMD predicted erosive disease only in women and that the rates of erosive disease were similar in both sexes (Forslind et al. 2003). Also Gossec et al found a similar proportion of erosive disease in women and men with RA, yet a higher percentage of women underwent joint surgery (Gossec et al. 2005).

Although joint destruction in RA is related to inflammation, other additional mechanisms may contribute to joint damage (Kirwan 2004) and, although the inflammatory activity is suppressed, joint damage may proceed and functional ability deteriorate over the years (Fex et al. 1996, Uhlig et al. 2000, Molenaar et al. 2004, Wick et al. 2004). Despite treatment, many patients still experience pain, fatigue and considerable disability (Pollard et al. 2005). In the Swedish TIRA cohort, function tended to slowly deteriorate over the years. The mean changes were, however, rather small and may not denote an important clinical difference. In the early phase of the disease, function is mostly affected by disease activity. Later on function is more influenced by structural damage than by inflammation (Guillemin et al. 1992, Scott et al. 2000a, Welsing et al. 2001).

***Table 12**. Mean values at different follow-ups for men and women respectively and p-value for difference between baseline and 3-year follow-up.*

	Inclusion (n=320) mean(SD)	**Year 1** (n=297) mean(SD)	**Year 2** (n=284) mean(SD)	**Year 3** (n=276) mean(SD)	p
Swollen joints(0-28)					
women	8.9 (6)	4.2 (5)	4.1 (5)	3.7 (5)	<0,0001
men	10.8 (6)	3.6 (4)	4.2 (5)	4.6 (4)	<0,0001
Tender joints(0-28)					
women	9.1 (7)	4.1 (5)	3.8 (5)	3.7 (5)	<0.0001
men	9 (7)	3.2 (3)	4 (6)	4 (6)	<0.0001
Morning stiffness (min)					
women	110 (73)	66 (73)	65 (70)	54 (67)	<0.0001
men	101 (64)	59 (59)	58 (64)	57 (62)	<0.0001
PGA (0-4)					
women	2 (1)	1.2 (1)	1.1 (0.7)	1.1 (0.8)	<0.0001
men	2 (1)	1 (0.6)	1.1 (0.7)	1.2 (0.8)	<0.0001
ESR (mm/h)					
women	35 (24)	24 (21)	22 (19)	21 (18)	<0.0001
men	33 (22)	21 (20)	22 (20)	23 (21)	<0.0001
CRP (mg/l)					
women	28 (27)	17 (23)	15 (21)	13 (16)	<0.0001
men	30 (28)	16 (18)	15 (17)	14 (18)	<0.0001
DAS28 (score)					
women	5.2 (1)	3.8 (1)	3.8 (1)	3.6 (1.4)	<0.0001
men	5.3 (1)	3.5 (1)	3.5 (1)	3.6 (1.4)	<0.0001
Wellbeing(VAS 0-100)					
women	45 (25)	39 (25)	37 (25)	35 (25)	<0.0001
men	40 (25)	32 (24)	32 (25)	35 (23)	NS
Pain (VAS 0-100 mm)					
women	48 (23)	40 (27)	36 (26)	36 (25)	<0.0001
men	47 (27)	34 (27)	34 (26)	35 (24)	<0.0001
Walking velocity (s)					
women	14.4 (7)	13.2 (5)	13.3 (6)	14 (6)	NS
men	13.6 (6)	12.3 (4)	14.5 (14)	13 (4)	NS
SOFI hand (0-16)					
women	2.4 (2)	1.8 (2)	1.9 (2)	2.1 (2)	NS
men	3.4 (3)	2.4 (2)	2.8 (2)	2.6 (3)	0.012
SOFI upper (0-12)					
women	0.9 (2)	0.8 (1)	0.8 (1)	0.9 (2)	NS
men	1.8 (2)	1.7 (2)	1.8 (2)	1.7 (2)	NS
SOFI lower (0-16)					
women	2.3 (2)	1.8 (2)	1.8 (2)	2 (2)	NS
men	2.2 (2)	1.7 (2)	1.8 (2)	1.7 (2)	NS
HAQ (0-3)					
women	0.9 (1)	0.73 (0.6)	0.7 (0.6)	0.78 (0.6)	0.001
men	0.8 (1)	0.44 (0.4)	0.5 (0.5)	0.4 (0.4)	<0.0001

HAQ is a powerful predictor of severe disease, total joint replacement, work disability and mortality (Drossaers-Bakker et al. 1999, Wolfe and Hawley 1998, Sokka et al. 1999, Pincus et al. 1984, Sokka et al. 2004). In the TIRA cohort, baseline scores of HAQ were strongly correlated to walking speed, lower limb function, grip force, patient's assessment of pain and wellbeing, DAS28, physician's global assessment of disease activity, and hand function. At the 1-year follow-up, HAQ correlated strongest to walking speed, lower limb function and grip force and these correlations persisted for HAQ at all follow-ups during the first 5 years. In general, correlations were weaker between HAQ and laboratory data. As expected, women had lower grip force compared to men and this may explain some of the gender differences in functional disability (Thyberg et al. 2005). There were, however, no gender differences regarding walking speed and lower limb function. Pain is the strongest determinant of HAQ, together with disease activity and muscle strength (Wolfe 2000, Sokka 2000, Häkkinen et al. 2006).

The SOFI index measures function in hands, upper and lower limbs. Generally, men had poorer SOFI scores regarding function of hands and upper limbs but not lower limbs, indicating that men are stronger but have less mobility, at least in hands and upper limbs (Björk et al. 2006). Similar gender differences in hand function are also seen in the general population (Björk et al. to be published).

The rapid initial improvements may be explained by early institution of DMARDs and the early multiprofessional treatment. The role of physiotherapy and occupational therapy in early disease is to maintain or improve mobility and physical functioning. This was not done according to any protocol, but instituted when judged appropriate. All patients, however, participated in a group educational programme as part of the TIRA study protocol.

After 3 years, almost 25% of the TIRA patients were in remission, but approximately 15% had sustained high or moderate disease activity during all 3 years, indicating that this group of patients are at most risk of poor outcome and are candidates for early targeted intense treatment.

Direct and indirect costs and predictors of high costs (papers II and III)

Direct costs

In this thesis work, considerable costs, both direct and indirect, were found to be incurred within the first year of the disease. Indirect costs were higher and accounted for more than 70% of total costs. Several studies have shown that work disability is the most expensive consequence of RA, and indirect costs exceed treatment costs in most studies (Meenan et al. 1987, Lubeck 1995, McIntosh 1996, Kobelt et al. 1999, Newhall-Perry et al. 2000, Jonsson and Husberg 2000, Leardini et al. 2002). Costs are typically higher in an inception cohort, due to frequent ambulatory care visits and high costs associated to numerous nurse visits for blood tests in the early course of disease.

In cost-of-illness studies performed before the era of biologic therapy, direct costs were dominated by hospitalisations and surgical interventions. Hospitalisation costs generally accounted for ≥ 60% of the total direct costs, and medication less than 20% (Pugner et al. 2000, Cooper et al. 2000a, Guillemin et al. 2004). In a Swedish population-based study of 82 patients from 1987, the total annual cost/patient was estimated to SEK 60 000 (Jonsson et al. 1992), corresponding to € 10 969, adjusted to 2001 values. This is rather close to the total cost/patient of € 11 495 assessed for year 3 after inclusion in the Swedish TIRA cohort. Jonsson et al found a significant correlation between increasing disability and costs. Patients with 'medium' disability had 30% direct costs and 70% indirect costs whereas patients with severe disability had substantially higher direct costs, mostly due to hospitalisation and surgery (Jonsson et al. 1992).

After the introduction of 'biologics', the total direct costs for rheumatoid arthritis have increased substantially and the distribution of costs has changed. In a study from the United States, the previous predominant costs of hospitalisation had decreased to 17% and drugs constituted the largest component of costs corresponding to 66% of the total direct costs (Michaud et al. 2003). In addition, most patients nowadays are treated primarily in ambulatory care, which shifts costs between inpatient and outpatient care. In the Swedish TIRA study, hospitalisation accounted for 12% of direct costs during year 1 and decreased to 5% during the third year. The costs for surgery, however, turned in the opposite direction and increased from 2% during the first year to 11% during year 3.

The number of outpatient visits tended to be underreported in the questionnaires (compared to the known visits according to the study

protocol and the drug monitoring protocol). A study from Germany compared patient-reported data with payer's source and found similar results with a high level of accuracy concerning medication and inpatient care, while physician visits and diagnostic tests were underreported (Ruof et al. 2004).

Costs for aids, devices and adaptations at home account for a substantial part of direct costs (Jaarsveld et al. 1998a). These non-medical costs differ substantially between countries, depending on the availability of devices and if they are subsidized by the society. In Sweden, these facilities are frequent and rather easily available and the greater part of costs is borne by the society. These non-medical costs were, however, omitted from our calculations due to incomplete data. This underestimates total direct costs and should be kept in mind when comparing the results reported here with those obtained in other studies.

Costs for complementary medicine are incurred by the patients since this is not covered by the health insurance in Sweden. Calculations of these costs may also differ between countries, depending on the definition of 'complementary medicine'. Some complementary treatments are recognized as medical treatments and costs are in some countries borne by the society.

The annual number of visits to physician in early RA differs between countries, due to different health care systems. A Dutch study calculated that patients had 9-10 visits to rheumatologist during the first year, dropping to 4-5 visits the following years. (Verstappen et al. 2004b). The average number of visits to physiotherapist in early RA was 12-16/year and to occupational therapist 2 visits/year (Verstappen et al. 2004b). During the first year, the Swedish TIRA patients made on average 5 visits to physician, mainly to a rheumatologist, 4 visits the second year and 2 visits during year 3. The visits to physiotherapist and occupational therapist were counted together and averaged 14 visits during the first year, 10 visits year 2, and 6 visits during the third year.

In the Swedish TIRA material, drugs accounted for only 9% of direct costs during the first year. The costs for safety monitoring, to detect possible adverse effects, must however be added. The numerous visits to the nurse for drug monitoring constitute a considerable part of the direct costs, especially in the early phase of the disease. The monitoring cost varies between different drugs, but usually amounts to higher costs than the drug itself (Prashker et al. 1995). These total costs of medication are substantial and do also comprise costs of

increasing drug dosage to maintain the intended treatment effect (Harrison 2003). On average the patients made 9 visits to the nurse during the first year. The number of visits dropped to 6 the second year, but did not drop further, indicating that the number of visits for safety monitoring were kept on that level. Women had significantly higher direct costs than men, due to more outpatient visits, more drugs, more surgery and more hospitalisation.

In univariate analysis, the best predictors of high direct costs were HAQ, hand function and lower limb function as measured by SOFI tests, walking speed, IgM-RF, anti-CCP, morning stiffness, DAS28, and the patient's assessment of pain. In the multivariate model, only HAQ and hand function remained significant together with IgM-RF. When SOFI tests and walking speed were excluded from the model, because of correlation to HAQ, only HAQ and IgM-RF remained as significant predictors. In numerous studies, functional disability has been the best predictor of high direct costs (Liang et al. 1984, Lubeck et al. 1986, Jonsson et al. 1992, McIntosh 1996, Singh et al. 1996, Clarke et al. 1997a, van Jaarsveld et al 1998a, Clarke et al. 1999, Yelin and Wanke 1999, Kobelt et al. 1999, Wong et al. 2001, Lapsley et al. 2002, Leardini et al. 2002, Michaud et al. 2003, Kavanaugh et al. 2004, Huscher et al. 2006). RF-positivity at the time of diagnosis and deteriorating HAQ during the first year in early RA has also been shown to predict high direct costs over the following years (Cooper et al. 2000b, Verstappen et al. 2004b).

Study designs and methods of calculating costs vary between studies. There is also a substantial variation in cost domains included in the calculations. The disease duration differs and changes in healthcare systems may occur over time (Rat and Boissier 2004, Rosery et al. 2005). Nevertheless, some comparisons can be made with recently published studies on patients with early RA (Table 13). For comparison, the costs for outpatient care include ambulatory care visits, radiographs and examinations, and the drug costs include monitoring costs. In the studies from the Netherlands, non-medical costs such as assistive devices and home adaptations, were excluded from the calculations. They constituted almost half of the total direct costs and were not included in the other studies. All costs are given in € 2001.

***Table 13**. The mean annual costs for 8 early arthritis studies. Costs are converted to € 2001.*

Author	year	N	Country	disease duration start/follow-up (years)	direct costs	indirect costs	proportion dir/indir costs %	distribution of direct costs %		
								outpatient care	inpatient care	drugs
Jaarsveld	1998	363	the Netherlands	<1 / 1-6	6846/3674*			34	41	25
Kobelt	1999	116	Sweden	<2 / 1-5	2145	6521	25 / 75	20	73	7**
Cooper	2000	171	UK	<1 / 1-5	924			9	56	35
Newhall-Perry	2000	150	USA	<1/ 0.5	3017	4240	42 / 58	56	5	39
Söderlin	2003	13	Sweden	<0.5 / 0.6	4957	4168	54 / 46	54	37	9
Verstappen	2004	96	the Netherlands	<1 / 1-2	5340/3122*			39	37	24
Merkesdal	2001	133	Germany	<1 / 2.5		12 414				
Puolakka	2006	162	Finland	<2 / 1		8154				

* non-medical costs making up for almost half of direct costs are excluded from the calculation of distribution of direct costs.
** only DMARDs

Indirect costs

For patients with RA, the working capacity is in danger from the very start of the disease (Sokka et al. 1999, Young et al. 2002, Puolakka et al. 2004). Rates of work disability differ between countries, but a prevalence of 20-50% during the first 3 years has been reported (Doeglas et al. 1995, van Jaarsveld et al. 1998b, Fex et al. 1998, Albers et al. 1999, Sokka et al.1999, Barrett et al. 2000, Merkesdal et al. 2001, Ödegård et al. 2005). With few exceptions (Merkesdal et al. 2001, Puolakka et al. 2005b), most studies have included only permanent work disability when calculating indirect costs, i.e. patients receiving disability pension due to work termination. However, and very importantly, the extent of sick leave accounts for a very large proportion of the indirect costs, since sick leave is very common, especially in early RA.

In the TIRA cohort, 81% of the indirect costs during the first year were due to sick leave. This emphasizes that costs for sick leave are substantial in early stages of the disease, while later on, costs for early retirement predominate. In the study from Finland (Puolakka et al. 2006), sick leave during the first year accounted for 89% of total work loss and decreased to 6% after 5 years, leaving 94% due to permanent work disability. In the German study (Merkesdal et al. 2001), 84% had sick leave days during the first year. This decreased to 25% during year 2 and patients with permanent work disability increased. The similar pattern was seen for the Swedish TIRA patients. During year 2 and 3, costs for sick leave decreased substantially, but was offset by increasing costs of early retirement, due to permanent work disability. At inclusion, younger patients were working to a higher extent than older patients. Approximately 80% of the patients below 35 years of age were working, compared to 40% in the group ≥ 35. This pattern persisted over time. In the 35-44-year group there was a slight increase in working capacity (Figure 12).

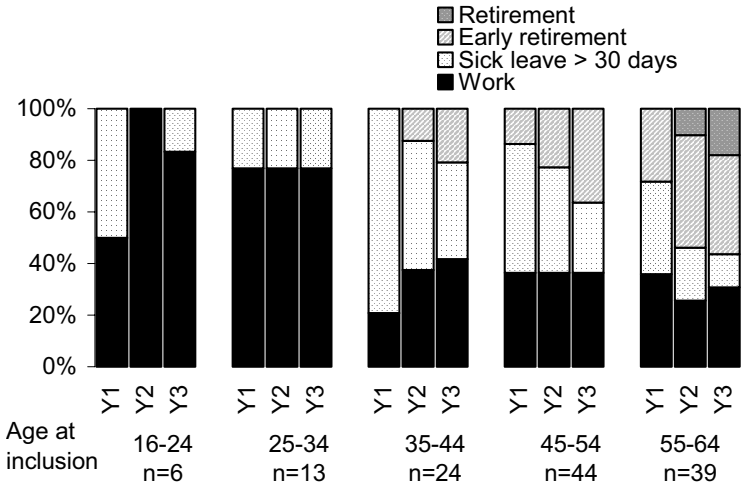


Figure 12. *Change in employment rate, sick leave and early retirement over the first 3 years in patients <65 years of age with complete data all 3 years (n=126).*

Some RA patients are retired already at the time for diagnosis (Fex et al. 1998, Barrett et al. 2000, Young et al. 2002). In the TIRA cohort, 18 patients (6%) of working age were already permanently work disabled at enrolment, and this further highlights the need for very early referral. The prevalence of work disability has been found to be 7 times as high in RA patients as in the general population (Albers et al. 1999).

In general, work disability rates have been higher in Europe compared to the United States, possibly as a consequence of different social benefit systems. In most European countries, costs are to a large extent borne by the society and less by the patient, and the access to benefits may be higher compared to the United States (Gabriel et al. 1997, Sokka 2003). In Sweden, the high rate of early retirement has recently become a political issue of high priority and the availability of welfare facilities is likely to become more limited in the future.

Despite differences between societies and patient cohorts, predictors of work disability are remarkably similar across studies and typically comprise functional disability, patient's assessment of pain and disease, educational level, physical job and age at onset (Reisine et al. 1995, Barrett et al. 2000, Sokka and Pincus 2001, Sokka 2003, Puolakka et al. 2005b). A recent review concluded that there is strong evidence that functional disability, physically demanding jobs, low education and high age are predictive factors of becoming work

disabled (de Croon et al. 2004). There was also inconsistent evidence that disease activity, pain, disease duration and female sex increased the chance of being work disabled (de Croon et al. 2004). Functional disability is by far reported as the most significant predictor of work disability. This was the case in the TIRA study and in accordance with numerous previous reports (Doeglas et al. 1995, Allaire et al. 1996, Gabriel et al.1997b, Fex et al. 1998, Wolfe and Hawley 1998, Kobelt et al. 1999, Albers et al. 1999, Sokka et al. 1999, Young et al. 2002, Leardini et al. 2002, Cooper et al. 2002, Kobelt et al. 2002, Verstappen et al. 2004a, Puolakka et al. 2005b, Ödegård et al. 2005). HAQ scores are significantly associated with employment, with a linear trend with higher HAQ scores giving progressively lower employment rates (Kavanaugh et al. 2004).

The patient's assessment of pain was also predictive of future work disability in the TIRA cohort and this is in agreement with previous studies (Allaire et al. 1996, Gabriel et al. 1997b, Wolfe and Hawley 1998, Sokka et al. 1999, De Roos and Callahan 1999, Merkesdal et al. 2001). Since pain correlates with disability as measured by HAQ (Sokka et al. 2000) and pain and joint mobility explain all 8 sub-dimensions in HAQ (Häkkinen et al. 2005), pain is, besides HAQ, likely to be a main reason for not being able to maintain working capacity. Pain is of great importance to patients, independent of disease duration (Ward and Leigh 1993) and is also the main concern for seeking medical help (Heiberg and Kvien 2002).

A lower educational level was associated with sick leave and work disability in the TIRA cohort, at least for patients below 55 years of age and this has also been reported by others (Douglas et al. 1995, Wolfe and Hawley 1998, Sokka et al.1999, Fex et al. 1998, De Roos and Callahan 1999, Verstappen et al. 2004a, Ödegård et al. 2005, Poulakka et al. 2005b). Given that educational level correlates to more physically demanding blue-collar jobs, patients with low educational level are more likely to stop working. Low formal educational level might also limit the possibilities of vocational training and this may also explain the association between low educational level and future work disability.

All indirect cost assessments in the TIRA study were based on patient-derived data without using external sources. This carries a possibility of recall bias. However, data from patient-reported questionnaires concerning sick leave and early retirement have recently been compared to health insurance databases. The results were comparable with no significant difference between patient-derived data and payer

data, indicating that patients adequately report their loss of productivity (Merkesdal et al. 2005).

Predictors of TNF-targeted therapy (paper IV)

The introduction of TNF-targeted therapy has dramatically improved the possibilities to treat patients with RA, but has also increased the direct costs considerably and introduced potential risks of serious adverse effects. Therefore, there is a need to identify the patients at most risk of an aggressive disease course with poor outcome and who will prosper from early instituted TNF-inhibitor therapy.

At the 5-year follow-up, 12% of the TIRA patients were prescribed TNF-inhibitors (TNF group) and they differed from patients not treated with TNF-inhibitors (non-TNF group) already from the beginning. The mean levels of anti-CCP were significantly higher in the TNF-group and all patients except one in the TNF group were anti-CCP positive, and all except one were SE+. Patients who were prescribed TNF-inhibitors were younger, had less co-morbidity and were more often women. The reasons for the different prescription patterns are not obvious, but may reflect a more severe disease in women. The reason why older patients received TNF inhibitors to a lesser extent than the younger could also be due to differences in disease severity, but is more likely to reflect the higher rate of co-morbidities and contra-indications against the use of biologicals.

The aim of the present study was to find an easy model to identify early predictors of future need for TNF-targeted therapy in recent-onset RA. Taking into account the potential risks and high costs of the new biological agents, it is desirable to find a model identifying 'true' candidates and minimizing the number of 'false-positive results'. Laboratory data in general, proved to be useful for men, in discriminating between patients receiving and not receiving TNF-inhibitor treatment and a model with baseline data was constructed. However, the number of men receiving TNF blockers in this study was too small to allow clear-cut conclusions. For women, DAS28>5.2 at the 3-month follow-up proved to be a valuable measure and could be used together with SE in an appropriate prediction model.

Several previous studies have shown that a positive anti-CCP antibody test at baseline predicts an aggressive disease course (Vencovsky et al. 2003, Forslind et al. 2004, Kastbom et al. 2004, Rönnelid et al. 2005, Lindqvist et al. 2005, Berglin et al. 2006). A high baseline level of anti-

CCP antibodies predicts more aggressive disease (Nell et al. 2005, Berglin et al. 2006) and this is supported by the finding that the average anti-CCP antibody level was significantly higher in the TNF group than in patients not treated with TNF inhibitors.

IgA-RF, which was included in the male model, has been claimed by others both to be of predictive value regarding future RA development (Rantapää-Dahlqvist et al. 2003) and of prognostic value regarding aggressive disease course and erosiveness (Houssien et al. 1998, Lindqvist et al. 2005).

Surprisingly, the baseline HAQ score did not add further information to the models after including laboratory data and DAS28. However, the HAQ scores at year 1 and 2 were significantly higher for both men and women in the TNF group. HAQ scores were only evaluated once a year, but since the scores had improved substantially at the 1-year follow-up, a 3-month HAQ-score would probably fit into the model and add discriminative information.

Genetic predictors as well as antibodies to CCP are particularly interesting because they can be found at the time of diagnosis, when interventions offer the greatest benefit. There was no increase in working capacity at the 3-year follow-up for patients treated with TNF-inhibitors. This was, however, not unexpected, since they had a disease duration of 2-3 years or more upon the institution of biologic pharmacotherapy. They were severely affected by the disease and most patients were already on long-term sick leave. After such a long period of sick-leave, few patients are likely to start working again and some have already received disability pension. The TNF-group in our cohort probably represents the patients who were most severely affected by the disease and who did not respond to treatment, despite previous efforts with different DMARDs. Failure to achieve early suppression of the disease and to have no response at the 6-month follow-up has been reported to be a strong predictor of permanent work disability (Puolakka et al. 2005a). A more rapid control of disease activity may very well have a potential to lower indirect costs and to some extent offset costs. A recent pilot-study showed that very early TNF-inhibitor treatment during 1 year in patients with poor prognosis provided a sustained response to therapy during the following 12 months after withdrawal of therapy (Quinn et al. 2005). The drug costs will further increase direct costs substantially, but potential savings can however be even larger since indirect costs are much higher than direct costs.

CONCLUSIONS

- Highly significant improvements were seen 3 months after the diagnosis of recent-onset RA, but although disease activity was well managed, function seemed to deteriorate slowly.

- Almost 25% of the patients went into remission (DAS <2.6) but approximately 15% had a sustained high or moderate disease activity during all 3 years.

- HAQ scores were similar for women and men at baseline, but had a less favourable course for women, and this gender difference remained over time. Women also had DMARDs more frequently prescribed.

- The average direct costs were €3,704 (US$ 3,297) year 1 and decreased to €2,652 (US$ 2,360) year 3. Drugs accounted for 9% of direct costs during year 1 and increased to 29% during year 3. Indirect costs were €8,871 (US$ 7,895) year 1 and remained essentially unchanged, similarly for both sexes.

- Women had higher direct costs compared to men, due to more ambulatory care visits, more surgery, and more complementary medicine.

- Functional disability and a high level of IgM-RF at inclusion, increased the odds of incurring high direct costs during the first year, and poor hand function and pain increased the odds of incurring indirect costs.

- All direct costs decreased over the years, except those for medication and surgery, which on the contrary increased.

- 50% of the patients <65 years of age were on sick leave or already early retired at inclusion. Costs for sick leave decreased, but this was offset by increased early retirement.

- Indirect costs were 2-3 times higher than direct costs all 3 years.

- Patients who were eventually prescribed TNF-inhibitors incurred higher direct and indirect costs even before prescription of anti-TNF therapy.

- At the 5-year follow-up (2001-2003), 12% of the patients were prescribed TNF-inhibitors. Baseline values of erythrocyte sedimentation rate, C-reactive protein, anti-CCP antibodies and morning stiffness were significantly higher in the TNF-group. These patients were also to a larger extent RF-positive and carried the shared epitope.

- Patients prescribed TNF-inhibitors were younger and a higher proportion was female.

- Based upon baseline and/or 3-months follow-up data on patients with recent-onset RA, two models are described (one for women and one for men) predicting later treatment with TNF-inhibitors. For men, a predictive model was constructed using baseline data including SE+, IgA-RF >100 U/L, and anti-CCP >240 U/L, yielding a specificity of 98% and a sensitivity of 71%. For women, the model comprised SE+ and 3-month DAS28>5.2, giving a specificity of 95% and a sensitivity of 59%.

SUMMARY IN SWEDISH/SAMMANFATTNING PÅ SVENSKA

Reumatoid artrit (RA) är en kronisk inflammatorisk sjukdom. I Sverige är prevalensen 0,5-0,7 % och kvinnor drabbas 2-3 gånger oftare än män. Sjukdomen påverkar funktionsförmåga och allmäntillstånd tidigt i sjukdomsförloppet och medför avsevärda ekonomiska konsekvenser såväl för den enskilde som för samhället.

Denna avhandling beskriver en 5-års uppföljning av 320 patienter med nydebuterad RA som, mellan januari 1996 och april 1998, inkluderats i den svenska multicenter-studien TIRA (*Tidiga Insatser vid Reumatoid Artrit).* Sjukdomsutveckling, funktion och kostnader har undersökts. Prediktorer för höga direkta och indirekta kostnader har kalkylerats och en algoritm har konstruerats för att prediktera framtida behov av TNF-hämmare hos patienter som inte svarar på traditionella sjukdomsmodifierande anti-reumatiska läkemedel (DMARDs).

Patienterna har följts regelbundet avseende kliniska och laboratoriemedicinska variabler, funktionsförmåga, smärta och välbefinnande. Därutöver har patienterna fyllt i hälsoekonomienkäter där all sjukvårdskonsumtion och sjukskrivning/förtidspension under föregående 6 resp 12 månader redovisats.

Tre månader efter påbörjad behandling sågs signifikanta förbättringar avseende sjukdomsaktivitet och funktionsförmåga, men 15 % av patienterna hade ihållande hög sjukdomsaktivitet trots konventionell behandling. Funktionsförmåga hos män förbättrades i mycket högre grad än hos kvinnor och efter 2 år stod signifikant fler kvinnor på remissionsinducerande medicin, vilket kan tyda på att kvinnor har en mer aggressiv sjukdom än män. Öppenvårdsbesök svarade för 76 % av direkta kostnader under första året. Kvinnor frekventerade läkare i signifikant högre grad än män och använde också mer komplementär medicin. Män >65 år hade låga sjukvårdskostnader jämfört med yngre män och jämfört med kvinnor i alla åldrar. Nedsatt funktionsförmåga och hög nivå av IgM-klass reumatoid faktor (RF) vid inklusion, var prediktivt för att generera höga direkta kostnader under det första året. Hög självskattad smärta och nedsatt handfunktion var prediktivt för att bli sjukskriven eller förtidspensionerad under år 1.

Indirekta kostnader var högre än direkta kostnader alla åren. Under år 1 var den genomsnittliga direkta kostnaden per patient SEK 34 258 (€3 704) och SEK 24 592 (€2 652) under år 3. Alla direkta kostnader minskade från år 1 till år 3, utom kostnader för läkemedel och kirurgi.

Indirekta kostnader var SEK 82 053 (€8 871) under år 1 och förblev väsentligen oförändrade över tid och lika för män och kvinnor. Drygt 50% av patienterna var sjukskrivna eller förtidspensionerade vid inklusion. Sjukskrivning minskade över tid men kompenserades av ökad förtidspensionering. Patienter med enbart grundskoleutbildning var i högre grad sjukskrivna/förtidspensionerade jämfört med dem som hade gymnasie- och universitetsutbildning.

TNF-hämmare blev tillgängliga under år 1999 och vid 3-års uppföljningen stod 14 patienter (5%) på dessa läkemedel. Detta ökade läkemedelskostnaden avsevärt. Jämfört med övriga patienter hade TNF-patienterna högre sjukdomsaktivitet vid studiestart och genererade högre kostnader redan före insättning av TNF-hämmare.
Vid 5-års uppföljningen (2001-2003) hade 31 patienter (12%) förskrivits TNF-hämmare. Utgångsvärden av "sänkan" (ESR), C-reaktivt protein (CRP), anti-CCP antikroppar och morgonstelhet var signifikant högre i denna grupp. Dessa patienter var också i högre utsträckning RF-positiva och bärare av 'shared epitope' (SE). Anti-TNF behandlade patienter var signifikant yngre och oftare kvinnor. För män, kunde en prediktiv modell konstrueras med utgångsdata omfattande SE+, IgA-RF >100 U/L och anti-CCP >240 U/L. Detta gav 98% specificitet och 71% sensitivitet. För kvinnor, visade sig "disease activity score" (DAS28) vid 3-månaders uppföljning vara en bättre prediktor och den slutliga modellen omfattade SE+ och 3-månaders DAS28>5.2 med 95% specificitet och 59% sensitivitet.

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