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Work capacity and productivity costs in early rheumatoid arthritis: A five-year prospective study

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Academic dissertation

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Cover figure: Adjusted risk for permanent rheumatoid arthritis (RA)-related disability pension by 6-month response group. I = clinical remission, II = ACR50 but no remission, III = ACR20 but not ACR50, IV = less than ACR20.

1 ABSTRACT 1

2 LIST OF ORIGINAL PUBLICATIONS 3

3 ABBREVIATIONS 4

4 INTRODUCTION 5

5 REVIEW OF THE LITERATURE 7

5.1 What is called rheumatoid arthritis (RA)? 7

5.2 Epidemiology of RA 8

5.3 Etiology 8

5.4 Pathogenesis of RA 8

5.5 Clinical manifestations of RA 9

5.6 Disability in RA 10

5.7 Assessment of RA 12
5.7.1 General 12
5.7.2 Measurement of disease activity and outcome 13
5.7.3 Tender and swollen joints 13
5.7.4 Pain score 13
5.7.5 Global assessments of RA severity 13
5.7.6 Acute-phase reactants 14
5.7.7 Stanford Health Assessment Questionnaire (HAQ) 14
5.7.8 Radiological assessment 15
5.7.9 Indices of RA activity 16
5.7.10 Psychological factors in RA 16
5.7.11 Assessment of overall RA impact: the ICF approach 17
5.7.12 Quality of life measures in RA 20
5.7.13 Evaluation of improvement 20

5.8 Economic burden of RA 21
5.8.1 General 21
5.8.2 Direct costs 21
5.8.3 Indirect costs 22
5.8.4 Intangible costs 22

5.9 Loss of work capacity in RA 23
5.9.1 General 23
5.9.2 Definition of ”work disability” 23
5.9.3 Occurrence of permanent work disability 26
5.9.4 Associations of permanent work disability 26
5.9.5 Difficulties in comparison of studies 30
5.9.6 Computation of loss of productivity 30

5.10 Treatment of RA 32
5.10.1 General 32
5.10.2 Traditional DMARDS 32

5.10.3 Role of glucocorticoids 33
5.10.4 Combination treatment 33
5.10.5 Biological agents 35
5.10.6 Impact of treatment on work capacity 35
5.10.7 Rehabilitation 37

5.11 Finnish social security system 37

6 AIMS OF THE STUDY 39

7 PATIENTS AND METHODS 41

7.1 Selection of patients and study design 41

7.2 Linking of items of HAQ to ICF categories 49

7.3 Statistical analyses 50

8 RESULTS 53

8.1 General 53

8.2 Work disability days (Study I) 55

8.3 Work disability benefits (I) 56

8.4 Loss of productivity (IV) 56

8.5 RA-related permanent work disability (I) 58

8.6 Gainfully employed patients (I) 59

8.7 Predictors of cumulative work disability (II) 59

8.8 Predictors of permanent RA-related disability pension (II) 60

8.9 Impact of early treatment response on maintenance of work capacity (III) 60

8.10 Association with loss of productivity (IV) 63

9 DISCUSSION 67

9.1 Monetary value of loss of productivity 67

9.2 Impact of early aggressive treatment with a combination of DMARDs on work capacity 70

9.3 Risk factors for diminished work capacity 72

9.4 Impact of treatment response on maintenance of work capacity 73

9.5 Socio- and pharmaco-economic implications 76

9.6 Can the results be generalized? 77

10 CONCLUSIONS 79

10.1 Answers to the questions 79
10.1.1 Impact of initial drug treatment strategy on work disability 79
10.1.2 Baseline predictors of cumulative work disability and productivity loss 79
10.1.3 Impact of treatment response on prognosis for work capacity 80
10.1.4 Monetary value of RA-related loss of productivity 80

10.2 Clinical implications 80

11 ACKNOWLEDGEMENTS 83

12 REFERENCES 85

13 APPENDICES 109

14 ORIGINAL PUBLICATIONS 119

1 ABSTRACT

Loss of work capacity is a serious consequence of rheumatoid arthritis (RA), and until recently, the rate of permanent work disability has been high despite development of antirheumatic therapy. The Finnish Rheumatoid Arthritis Combination-Therapy Trial (FIN-RACo), begun in 1993, provided an opportunity to investigate the impact of antirheumatic drug treatment on the maintenance of work capacity and to explore risk factors for decreased ability to work. The national social insurance registers offered objective data on sick leaves and longer-term work disability and enabled estimation of the monetary value of this outcome with high accuracy.

In the FIN-RACo trial, 195 patients with recent-onset, active RA were randomized to receive either a combination of disease-modifying antirheumatic drugs (DMARDs) (sulfasalazine, methotrexate, hydroxychloroquine) and prednisolone, or a single DMARD with or without prednisolone for 2 years, after which, drug-treatment strategy became unrestricted. The patients were followed up with regular check-up visits for 5 years. The present study focuses on the 162 patients who were working or at least available for work at baseline. After a 5-year followup, data on sick leave and retirement came from social insurance registers or case records. The cumulative duration of sickness allowance periods and RA-related disability pensions was calculated for each patient.

The cumulative number of work disability days per patient-observation year was significantly lower in the combination-therapy group than for patients who initially received a single-DMARD therapy; sex- and age-adjusted medians (95% confidence interval, CI) were 18 days (5–31) and 37 days (24–50), respectively (P = 0.009).

The monetary value of productivity loss due to RA-related days off work was estimated on the basis of sickness allowances paid, which, in turn, had been calculated according to individual incomes assessed by Finnish tax authorities. A total of 120 (75%) patients, women more often (82%) than men (61%), used sick leave or experienced longer-term work disability, or both, which led to loss of productivity. The value of annual productivity of those 120 patients averaged US$35,991 (95% CI 32,762–39,221). By the human capital approach, mean lost productivity per patient-year for the group of 162 patients was $8,805 (95% CI 6,784–11,160). The value of lost productivity was highest during the first year, resulting mainly from sick leave (89%); thereafter, permanent work disability dominated.

Loss of productivity was inversely related to improvement in RA over the followup, and was associated with increase in number of erosions. Even a slight functional disability as measured by the Stanford Health Assessment Questionnaire (HAQ) at 6 months led to increased age- and sex-adjusted odds for higher productivity losses. When the HAQ was linked to the International Classification of Functioning, Disability, and Health (ICF), “changing and maintaining body position” was the only ICF subcategory independently associated with loss of productivity.

High scores (≥50) in patient’s and in physician’s global assessment of RA severity (visual analogue scale, VAS 0 to 100) appeared as baseline risk factors for extension of work disability, in addition to low education level (<10 years of schooling), older age, and high HAQ score (≥ 1.0). Combination therapy was a protective factor.

Early treatment response had a strong impact on maintenance of patients' work capacity. None of the 44 patients in remission at 6 or 12 months became permanently work disabled over the 5-year followup, whereas 56% of the patients without 20% improvement at 6 months ended on a permanent RA-related disability pension.

2 LIST OF ORIGINAL PUBLICATIONS

I. Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blåfield H, Hakala M, and Leirisalo-Repo M, for the FIN-RACo Trial Group. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: A five-year randomized followup trial. Arthritis & Rheumatism 2004;50:55-62.

II. Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Hakala M, Korpela M, Ilva K, Yli-Kerttula U, Piirainen H, and Leirisalo-Repo M, for the FIN-RACo Trial Group. Predictors of productivity loss and work disability in early rheumatoid arthritis: A 5-year follow up study. Annals of the Rheumatic Diseases 2005;64:130-133.

III. Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Hakala M, Järvinen P, Ahonen J, Forsberg S, and Leirisalo-Repo M, for the FIN-RACo Trial Group. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: Five-year experience from the FIN-RACo trial. Arthritis & Rheumatism 2005;52:36-41 .

IV. Puolakka K, Kautiainen H, Pekurinen M, Möttönen T, Hannonen P, Korpela M, Hakala M, Arkela-Kautiainen M, Luukkainen R, and Leirisalo-Repo M. Loss of productivity in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: A five-year followup study. Submitted.

3 ABBREVIATIONS

ACR	American College of Rheumatology
ANOVA	analysis of variance
ARA	American Rheumatism Association
CI	confidence interval
COBRA	Combinatietherapie Bij Rheumatoïde Arthritis Study
CRP	C-reactive protein
DAS	disease activity score
DAS28	disease activity score with 28 joints examined
DMARD	disease-modifying antirheumatic drug
EC	external criterion
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FCA	friction cost approach
FIN-RACo	Finnish Rheumatoid Arthritis Combination-Therapy Trial
HAQ	Stanford Health Assessment Questionnaire
HCA	human capital approach
HR	hazard ratio
ICD	International Classification of Diseases
ICIDH	International Classification of Impairments, Disabilities, and Handicaps
ICF	International Classification of Functioning, Disability, and Health
IP	interphalangeal (joint)
IQR	interquartile range
MCP	metacarpophalangeal (joint)
OR	odds ratio
PIP	proximal interphalangeal (joint)
PR	patient-reported
RA	rheumatoid arthritis
RF	rheumatoid factor
TNF-α	tumor necrosis factor- α
VAS	visual analogue scale
WHO	World Health Organization

4 INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown etiology characterized by chronic synovial joint inflammation causing pain, stiffness, and impaired function. Formation of rheumatoid pannus, an inflammatory and invasive tissue, eventually leads to joint destruction. Because of the lack of any specific feature or test, RA diagnosis is a composite of clinical and investigational features. For research purposes, the generally approved classification criteria used are the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for RA (Arnett et al. 1988). Rheumatoid arthritis occurs worldwide, affecting about 1% of the population (Silman 2001), but is rare in less developed rural parts of the world and more common in industrialized countries (MacGregor and Silman 2003).

The course of RA varies, but in clinic-based cohorts it is most often progressive with more or less continuous disease activity and tissue damage. This chronic nature of RA frequently results in functional disability of various degrees with considerable consequences for the patients as well as for society (Conaghan et al. 1999, Griffith and Carr 2001, March and Lapsley 2001). For patients of working age, diminished ability to perform their current jobs and cessation of working life are frequent and serious outcomes occurring early in the course of the disease (Shanahan and Smith 1999, Sokka 2003). For permanent work disability, older age, fewer years of schooling, a physically demanding job, and longer duration and severity of RA are among the most common risk factors (Reisine et al. 1995, Mau et al. 1996, Wolfe and Hawley 1998, Sokka and Pincus 2001,Young et al. 2003, Verstappen et al. 2004, de Croon et al. 2004). Wide agreement prevails that the most expensive consequence of RA is loss of productivity (Pugner et al. 2000, Cooper 2000, Ruof et al. 2003). Previous studies have, with few exceptions, evaluated only productivity lost because of permanent inability to work. Sick leaves have been included in analyses in only three studies. In two studies of early RA, monetary estimations were based on the average income of all gainfully employed persons in that particular country (Merkesdal et al. 2001, Hallert et al. 2004). The third study utilized individual income data to estimate productivity losses in a cohort with a mean RA duration of 8.4 years (Ruof et al. 2003).

The bulk of evidence indicates that disease-modifying antirheumatic drugs (DMARDs) not only relieve symptoms of RA but also improve long-term outcome, including limitation in radiographic damage and maintenance of good physical function (Fries et al. 1996, van der Heijde et al. 1996, Munro et al. 1998, Abu-Shakra et al. 1998, Stenger et al. 1998, Pincus and Sokka 2001). Some studies show that treatment with a combination of DMARDs provides a better response than does single-DMARD therapy (O´Dell et al. 1996, Boers et al. 1997, Calgüneri et al. 1999, O'Dell et al. 2002). In the Finnish Rheumatoid Arthritis Combination-Therapy Trial (FIN-RACo), a randomized clinical trial conducted from 1993 to 2000, the patients with recent-onset RA treated for 2 years with a combination of three DMARDs and prednisolone achieved significantly more remissions at 2 years than did those who received a single DMARD with or without prednisolone (Möttönen et at. 1999). Further, the aggressive initial combination therapy was superior in limiting peripheral joint damage for at least 5 years (Korpela et al. 2004). Until lately, no clear evidence has emerged that treatment improvements have altered the rate of work disability (Allaire 2001), but recent study shows an association between higher employment rates and etanercept use (Yelin et al. 2003).

The present study is a prospective cohort substudy of the FIN-RACo. A total of 162 patients with recent-onset RA, aged 18 to 65 and available for the workforce at study entry, were followed up for 5 years. Data on sick leaves and disability pensions came from the registers of the Social Insurance Institution and the Central Pension Security Institute. Individual incomes before contracting RA were calculated on the basis of the amount of sickness allowance. The cumulative number of RA-related work disability days per patient-year were calculated; loss of productivity by the human capital approach (Koopmanschap and Rutten 1996) was estimated for each patient. Baseline predictors and impact of drug treatment response on the outcomes underwent analysis.

5 REVIEW OF THE LITERATURE

5.1 What is called rheumatoid arthritis (RA)?

Because rheumatoid arthritis has variable clinical features, lacks any pathognomonic sign, symptom, or laboratory test, and is of unknown etiology, we must define by convention what we mean by "rheumatoid arthritis." Generally applied classification criteria are needed for the proper conduct of studies as well as for comparison and interpretation of results. The currently accepted classification scheme for rheumatoid arthritis is based on the 1987 American College of Rheumatology (ACR, formerly the American Rheumatism Association, ARA) criteria (Arnett et al. 1988, Table 1). These criteria fail, however, to rule out the possible heterogeneous etiology of clinical RA.

Table 1. American College of Rheumatology (ACR) 1987 classification criteria for RA.
For classification purposes, a patient has RA if at least four of the seven criteria are satisfied.

Criterion	must have been present for at least 6 weeks
1 Morning stiffness of ≥ 1 hour	+
2 Arthritis in 3 or more joint areas[1]	+
3 Arthritis in a hand joint (PIP, MCP, wrist)	+
4 Symmetric swelling of 1 joint area (as defined in 2)	+
5 Rheumatoid nodules	
6 Positive rheumatoid factor (RF)	
7 Radiographic changes in hand and/or wrist joint[2]	

[1] Right or left proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and metatarsophalangeal (MTP) joints.

[2] Erosions or periarticular osteopenia present.

5.2 Epidemiology of RA

RA prevalence has been between 0.5% and 1.0% in studies across Europe, North America, Asia and South Africa (Silman 2001). In the Finnish Mini-Finland study carried out during 1978-80, the prevalence of seropositive RA in the population ≥30 years of age was 0.8% (Aho et al. 1989 and 1998). Most studies have found a female-to-male excess of 2- to 4-fold. In all studies, age-specific prevalence rates increased with age.

The annual RA incidence in Finland was 39/100,000 in 1980 and 1985, and 32/100,000 adults in 1990 and 1995 (Kaipiainen-Seppänen and Aho 2000, Kaipiainen-Seppänen 2004). Between 1975 and 1995 in Finland, the peak of incidence rose by 9 years and peaked in 1995 in the age-group 65 to 74 (Kaipiainen-Seppänen et al. 1996). Despite this possibly declining incidence, the growing number of older people means an increasing number of individuals with RA. Incidence in females is greater than in males, with the exception of the oldest age groups.

5.3 Etiology

The etiology of RA is unknown, but both genetic and environmental factors are of significance in its initiation and perpetuation (Carty et at. 2003, Klareskog et al. 2004). Its familial nature has long been known. Siblings of persons affected with RA have a 2- to 4-fold risk for developing the disease when compared with unrelated individuals. Smoking has been a risk factor for RA both in cross-sectional and longitudinal studies (Aho and Heliövaara 2004), and it also worsens disease outcome.

5.4 Pathogenesis of RA

Immunological events are typical for RA pathogenesis (Ollier et al. 2001). The vast majority of scientists are of the opinion that the initiation of RA is a T cell-mediated, antigen-specific process (Firestein 2003). The arthritogenic agent may be a retrovirus, a bacterial product, or some other organism. In a susceptible host, an early T cell response results in production of T cell cytokines and, consequently, in recruitment of other inflammatory cells into affected tissues. The synovium becomes a locally invasive and destructive “pannus” which is

responsible for the marginal erosions at the synovial interface of cartilage and bone characteristic of RA. Immunoglobulins with rheumatoid factor (RF) activity are secreted in 70 to 90 % of patients (van Paassen et al. 2003).

5.5 Clinical manifestations of RA

RA is a systemic disease, but the most prominent feature is arthritis with typical symptoms of inflammation: *tumor, calor, dolor, functio laesa* (swelling, local heat, tenderness, and limited range of movement with stress pain) (Gordon and Hastings 2003, Woolf 2003). Erythema (*rubor*) of a joint is not, however, characteristic. The most common presentation is symmetric arthritis of the small peripheral joints. Other synovial structures—tendon sheaths and bursae, are also frequently affected. Onset may be acute, subacute, episodic (palindromic), or insidious, the latter being the most common type. Morning stiffness of joints lasting for at least an hour is one of the ACR 1987 classification criteria. Constitutional symptoms of inflammation such as fatigue, weight loss, and even fever are common and may occur early in the course.

The clinical course of RA is variable. It may sometimes be self-limiting or episodic but mostly is prolonged and progressive, resulting in increasing joint damage and destruction recognized clinically or radiologically (Ollier et al 2001). Clinical observations include reduced range of movement, collateral instability, malalignment, and subluxation with characteristic deformities especially in the hands and the feet. The key radiographic findings include fusiform soft tissue swelling, regional or periarticular osteoporosis, marginal or central osseous erosions and cysts, and diffuse loss of joint space. The development of joint destruction starts early and is most rapid during the first months of RA (Larsen and Thoen 1987, van der Heijde et al. 1992). The foot joints are usually affected earlier and in larger numbers than are the hand joints. Several scoring systems exist for radiographic evaluation of RA abnormalities.

Some studies report that the outcome of RA in women is worse than in men (Kuiper et al 2001); on women, disability and disease activity scores tend to be higher (Hallert et al. 2003, Tengstrand et al. 2004), with no gender difference in radiographic joint damage.

Inflammation may extend beyond synovial structures, causing nodules, sicca complex, serositis, and vasculitis (Matteson 2003). Osteoporosis of both the appendicular and axial skeleton develops early (Green and Deodrah 2001), and diffuse interstitial pulmonary fibrosis may occur. An elevated risk for coronary heart disease is associated with RA, and patients show higher mortality rates than in the general population with cardiovascular disease the most common cause of death (Mutru et al. 1985, Myllykangas-Luosujärvi et al. 1995).

5.6 Disability in RA

Inflammation of joints and other synovial structures, joint damage, and constitutional symptoms of RA lead to such problems as restriction in joint motion and decline in muscle strength, in a word: impairment of body functions (Stucki and Kroeling 2000, Gordon and Hastings 2003). This results in diminished capacity to perform tasks and, furthermore, to participate in social relationships.

The traditional biomechanical concept of disability includes only impaired physical functioning measured by clinical judgment, by observing patient performance, or by patient-reported assessment (van Gestel and Stucki 1999). Self-report questionnaires are the most popular instruments, although discrepancies may occur between patient-reported performance and actual performance. The Stanford Health Assessment Questionnaire (HAQ) (Fries et al. 1980) is the most widely used questionnaire for RA patients (see section 5.7). In early RA, HAQ disability is mainly a result of inflammation and pain, whereas the significance of structural damage as a cause of disability tends to grow progressively over time (Scott et al. 2000, Welsing et al. 2001). Only a minor correlation between HAQ disability and disease duration exists, however, and persistent variation in disease activity remains the major determinant of disability (Wolfe 2000, Kirwan 2001). Baseline factors associated with adverse prognosis for functional capacity have been explored in many studies (Ollier et al. 2001, Combe et al. 2003). In all studies reported, the HAQ disability itself has been a risk factor. Other predictors of future functional disability include older age, female gender, positive rheumatoid factor, and more joints affected (Harrison et al. 1996, Wiles et al. 2000, Hallert et al. 2003).

Physical disability impacts on social and personal aspects of life, resulting in handicap (Griffith and Carr 2001). People with RA differ from controls in their number of household chores, shopping and errands, social relations, leisure pursuits, and public-service activities (Yelin et al. 1995). Patients of working age often experience diminished work capacity and even total work disability (see section 5.9). Katz (1995) found in a prospective study that people with RA, when compared with controls, could perform fewer "value activities" at the commencement of the study. Over a 5-year period, these RA patients suffered an approximately 10% further reduction in these activities compared to controls' activities.

Various factors in a patient's life interfere to magnify each other. The loss of functional capacity and chronic pain associated with RA have profound effects on psychological well-being and on interpersonal relationships (van der Heide et al. 1994, Newman and Mulligan 2000). RA patients report more symptoms of depression than does the general population (Frank et al. 1988). On the other hand, psychosocial factors may significantly impact individual performance, e.g., HAQ disability (Scharloo et al. 1999, Escalante and del Rincón 1999).

The proportion of severely crippled RA patients in the community has decreased in the last decades. In the 1930s, of those with chronic arthritis selected from the Finnish population, 41% were "totally disabled" (Holsti and Rantasalo 1936), but in 1989, of RA patients in Kuusamo, Finland, only 10% were "severely incapacitated" (Hakala and Nieminen 1996). The reasons for this favorable development are diverse. Multidisciplinary care including early treatment with DMARDs may have improved the prognosis for RA (Hakala et al. 1994b). The most likely explanation, however, is orthopedic surgery and the advent of joint replacement operations on large joints.

The consequences of a disease have been classified as a flow chart of impairment→disability →handicap in the former International Classification of Impairments, Disabilities, and Handicaps (ICIDH) of the World Health Organization. This classification has been revised to become the International Classification of Functioning, Disability, and Health (ICF; WHO 2001) which further extends the scope of disability and allows description of the remaining capabilities and of contextual factors (see section 5.7.10).

The results of a disease can also be represented by the term “quality of life.” This can be regarded as a subjective understanding of the disease-related overall situation, compared to the more objective picture of the ICF approach. Reduced quality of life comes close to the concept of handicap. No overall agreement exists on how to define quality of life, and many non-equivalent instruments serve for measurement. (Scott and Garrood 2000). The concept of quality of life has become a cornerstone of health economics; cost-utility analysis of interventions is based on measures of quality of life in terms of quality-adjusted life years (Homik and Suarez-Almazor 2004).

5.7 Assessment of RA

5.7.1 General

The ability of a physician to take a clear history and perform a competent clinical examination is a starting point both of proper diagnosis of RA and of evaluation of any patient with RA. Evaluation can be divided into assessment of process, i.e., what happens during the course of the disease, and assessment of outcome or “end result”, i.e., cumulative consequences of the disease process (van Gestel and Stucki 1999, Pincus and Sokka 2003, Stucki and Sigl 2004).

The process measurements reflect current disease activity, and they fluctuate during the course of RA, whereas the outcome measurements gradually worsen. Outcome variables include joint erosions, function and disability, social, psychological and economic consequences, and mortality. Function and disability, however, contain aspects of both process and outcome. In early RA, function is impeded mainly by the impact of joint inflammation and is thus predominantly a process variable. In established disease, however, joint damage is a progressively more important cause of limitations, and function is predominantly an outcome variable (Scott et al. 2000). For all assessment, it is important to use a valid and standardized measure which is feasible, reproducible, and sensitive to change (Guillemin 2003). However, many measures used are influenced by psychosocial factors and comorbidities (McFarlane and Brooks 1997)

5.7.2 Measurement of disease activity and outcome

No single measure available covers all aspects of RA activity. Various approaches undertaken have led to selection of a core set of measurements to be included in clinical trials (Felson et al. 1993, Tugwell and Boers 1993). As a result of international cooperation, the consensus reached as to the minimal set of measures to be included in RA clinical trials is as follows: a set of six process variables—number of tender joints, number of swollen joints, pain score on a visual analogue scale (VAS), patient's global assessment of severity of RA on VAS, assessor's global assessment on VAS, acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein)—and two outcome variables—functional capacity by the Stanford Health Assessment Questionnaire (HAQ) and radiographic assessment of the joints of the hands and feet (Buchbinder et al. 1995, van Riel 2000).

5.7.3 Tender and swollen joints

Detection of joint inflammation is central to assessment of disease activity (Woolf 2003). An inflamed joint is typically tender and swollen, two characteristics, each providing different information: Tenderness is more sensitive to change and correlates with pain, whereas swelling correlates with acute phase reactants and radiographic progression (van Riel 2000).

5.7.4 Pain score

Patients with RA usually report pain as their worst problem (Sokka 2003a). In measuring pain levels, the Visual Analogue Scale is the instrument most frequently used. The VAS is easy to use and, because of its continuous scale, sensitive to change. Further, it can be interpreted as a ratio scale. The ACR recommends the use of a 10 cm horizontal VAS with "no pain" at one end and "worst possible pain" at the other.

5.7.5 Global assessments of RA severity

Patient's and physician's global assessment of RA severity measured on a VAS have, in clinical trials of RA, appeared to be the measures most sensitive to change, showing good

discriminative power, and being predictors of future disability (Wolfe and Cathey 1991, Buchbinder et al. 1995). The global measures are a type of sum indicator reflecting a patient's status wider than merely physiological characteristics. Pain, depression, HAQ disability, or number of tender joints were correlates of patient's global assessment of RA severity in one followup study (Smedstad et al. 1997). In the multivariate approach, however, only pain and depression retained a statistically significant impact on patient's global assessment. A discrepancy may exist in the perception of RA activity between patient and physician. A patient's global assessment lower than the physician's was associated in a Brazilian study with low education (Nicolau et al. 2004).

5.7.6 Acute-phase reactants

Erythrocyte sedimentation rate (ESR, Westergren method, mm in the first hour) and C-reactive protein (CRP, mg/L) are non-specific measures of inflammation, but correlate with other disease activity variables and are sensitive to change (van Riel et al. 2000). ESR reflects the disease activity of the past few weeks, while shorter-term changes in activity are shown by CRP, which is less susceptible than ESR to disturbing factors. Time-integrated values of CRP correlate with progression of radiological damage (Plant et al. 2000).

5.7.7 Stanford Health Assessment Questionnaire (HAQ)

The disability index of the HAQ is a self-assessment questionnaire to determine the ability of a patient to perform several daily activities over the previous weeks (Fries et al. 1980, Table 2, section 5.7.10). It contains 20 questions divided into 8 subdimensions. Each question has four options for answering scored from 0 to 3; these are activities performed: without ANY difficulty (score of 0), with SOME difficulty (score of 1), with MUCH difficulty (2), and UNABLE to do (3). If the patient needs aids or devices or help, the specific activity is given a score of 2. Maximum scores per subdimension are added up and then divided by the number of subdimensions provided (at least six). The Finnish version of HAQ has been used since the early 1990s (Hakala et al. 1994a).

The HAQ is short, easy to process, and reliable, and is validated against many other variables. Several studies show its value in assessing short-term response to treatment (Bruce and Fries 2003). Interpretation of HAQ score depends on disease stage, since aspects of disease activity as well as aspects of disease outcome will influence physical disability. In early RA, HAQ disability is mainly determined by inflammation and pain, but the effect of structural damage grows progressively over time (Scott et al. 2000, Welsing et al. 2001). Involvement of different joint areas makes differing contributions to overall disability (Wiles et al. 2000). In studies on groups of early RA patients, the HAQ improves after start of drug therapy, reflecting treatment response and perhaps adjustment to the situation; on average, a steady increase at a slow rate occurs thereafter. The HAQ score of an individual patient has, however, a very variable course which is mainly determined by changes in disease activity (Kirwan 2001). Several patterns of longitudinal course of the HAQ – non-linear, chaotic and non-time-determined – are defined by Wolfe (2000). Pain is the most powerful individual determinant of the HAQ (Sokka et al. 2000), which is also associated with age, gender, and psychosocial factors (Smedstad et al.1995, Scharloo et al. 1999, Escalante and del Rincón 1999, Wolfe 2000). Some modifications of the original HAQ have been developed (Wolfe 2001).

Pincus et al. (2003) have shown that the pooled index of the patient questionnaire Core Data Set measures—patient's global assessments, pain score, and the HAQ—appears to be as informative as are the pooled indices of all Core Data Set measures and of the assessor-derived ones in distinguishing between active treatment and placebo.

5.7.8 Radiological assessment

X-ray progression in RA is used both to follow the course of the disease by an objective measure and to assess long-term effects of treatment (Ory 2003). In longitudinal analysis, fluctuations in RA activity were related to changes in radiological progression, supporting the concept that disease activity causes radiological damage (Welsing et al. 2004). Many methods of radiographic assessment have been devised; among them, the Sharp and the Larsen scoring systems and their modifications (Sharp et al. 1971, Larsen et al. 1977), the most widely used, focus on the small joints of the hand and foot. The Larsen method scores radiological appearances of joints in the hands, wrists, and feet compared to a set of reference films for each joint. The joints scored on each side are I IP, II-V PIP, and I-V MCP in the hands, I IP and II-V

MTP in the feet, and the wrist as one joint. The range of score for each joint is from 0 to 5: normal appearance (0), slight abnormality (1), definite early abnormality (2), medium destructive abnormality (3), severe destructive abnormality (4), and mutilating abnormality (5). In calculating the total Larsen score, all individual joint scores are summed after multiplying the wrist scores by 5. The maximum total score (Larsen index) is 200 per patient.

In addition to radiography, new techniques are available for imaging in RA, such as magnetic resonance imaging and ultrasound. Their exact place in RA diagnosis and assessment require still more research (van der Heijde 2003).

5.7.9 Indices of RA activity

Variables in the core data set have been combined in indices of disease activity to provide a single outcome measure (Pincus and Sokka 2003). The Disease Activity Score (DAS) and the DAS28 are used widely in Europe. The DAS is a statistically derived index combining tender joints, swollen joints, ESR, and patient's global assessment of disease activity and is based on treatment decisions of rheumatologists in daily clinical practice (van der Heijde et al. 1993). The original DAS is calculated by a 44-joint count for tenderness and swelling, while the more concise DAS28 is based on examination of 28 joints (Prevoo et al. 1995).

5.7.10 Psychological factors in RA

In addition to physical symptoms and signs, RA makes a marked impact on a patient's emotional and social functioning. On the other hand, all the effects of the disease are influenced by the individual's psychological characteristics which determine adaptation to the chronic disease and its consequences (Smedstad et al. 1995, Newman and Mulligan 2000). For instance, much of the variation in HAQ remains unexplained by disease activity and radiographic score alone (Escalante and del Rincon 1999, Wolfe 2000, Sokka et al. 2000) and is probably influenced by psychological variables, such as self-efficacy, self-esteem, anxiety, depression, learned helplessness, locus of control, coping, and social support. Coping strategies and different types of illness perception have been shown in RA to contribute to health

outcomes (Scharloo et al. 1999). High self-efficacy scores were associated with favorable changes in health status measures over a 2-year followup (Brekke et al. 2001).

5.7.11 Assessment of overall RA impact: the ICF approach

To examine the entire bio-psycho-social impact of RA, the International Classification of Functioning, Disability, and Health (ICF) can serve as a valuable tool (Cieza and Stucki 2004, Stucki and Cieza 2004, Scott et al. 2005). The ICF was developed by the World Health Organization (2001) to provide a systematic coding scheme and a universal language for describing situations with regard to human functioning and its restrictions. The ICF organizes information into two parts, each with two components: 1) Functioning and Disability: a) Body Functions and Structures, b) Activities and Participation; and 2) Contextual Factors: c) Environmental Factors, d) Personal Factors. Thus, the ICF offers a comprehensive framework covering not only disease consequences but also other characteristics of patients themselves and of the environment, all of which play an important role in any possible misfit between individual capability and environmental requirements, a misfit leading to disability in general and to work disability especially (Shanahan and Smith 1999, Cieza and Stucki 2004) (Figure 1).

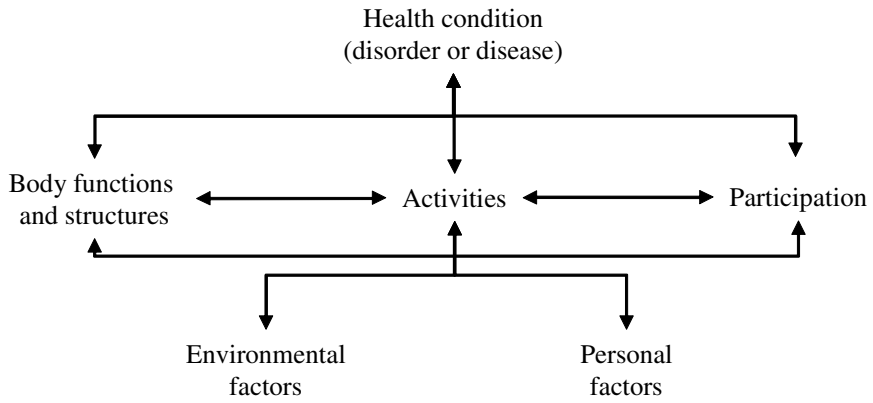

Figure 1. Interactions between components of the International Classification of Functioning, Disability, and Health (ICF). (Reprint with permission from the WHO).

The ICF in itself is not a measure of functioning, but information gathered by history or by any available generic or RA-specific questionnaire can be linked to the system of the ICF (Cieza et al. 2002). Table 2 shows the items of the HAQ linked to categories and subcategories of the ICF.

Table 2. Questions from the Stanford Health Assessment Questionnaire (HAQ) disability index linked to (sub)categories of the International Classification of Functioning, Disability, and Health (ICF).

HAQ question	ICF code	ICF category	Subcategory of "mobility"
Are you able to:			
- Dress yourself, including tying shoelaces and doing buttons?	d540	SC	-
- Shampoo your hair?	d510	SC	-
- Stand up from a straight chair?	d410	MOB	BP
- Get in and out of bed?	d410	MOB	BP
- Cut your meat?	d550	SC	-
- Lift a full cup or glass to your mouth?	d445	MOB	HA
- Open a new milk carton?	d445	MOB	HA
- Walk outdoors on flat ground	d450	MOB	MOV
- Climb up five steps?	d455	MOB	MOV
- Wash and dry your body?	d510	SC	-
- Take a tub bath?	d510	SC	-
- Get on and off the toilet?	d530	SC	-
- Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	d430	MOB	HA
- Bend down to pick up clothing from the floor?	d410	MOB	BP
- Open car doors?	d445	MOB	HA
- Open jars which have been previously opened?	d445	MOB	HA
- Turn faucets on and off?	d445	MOB	HA
- Run errands and shop?	d620	DL	-
- Get in and out of a car?	d470	MOB	MOV
- Do chores such as vacuuming or yardwork?	d640	DL	-

MOB = Mobility category

BP = Subcategory "Changing and maintaining body position"

HA = Subcategory "Carrying, moving and handling objects"

MOV = Subcategories "Walking and moving" and "Moving using transportation"

SC = Self-care category

DL = Domestic life category

5.7.12 Quality of life measures in RA

Health-related quality of life is a different approach to the impact of RA (Guillemin 2000), and its measurement relies mainly on self-administered questionnaires (Scott et Garrood 2000). In addition to their use as outcome measures, these instruments form the basis of cost-utility analysis in health economics (Homik and Suarez-Almazor 2004).

5.7.13 Evaluation of improvement

In intervention studies, improvement in RA is the main target and is the most important factor to evaluate. Two sets of treatment response criteria have been developed: the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) criteria. Both methods are valid in clinical trials, both being able to discriminate between treatments and correlating with other disease variables, both process and outcome (Pincus and Sokka 2003). The ACR criteria for improvement are based on changes in the ACR Core Data Set measures (Felson et al. 1995). The baseline requirement is that all these measures should have values higher than 0 at study entry. The ACR20 response requires at least a 20% improvement in tender (68 counted) and swollen (66 counted) joint count plus a similar improvement in at least three of the five remaining core measures (patient's and physician's global assessments of the severity of RA, patient's assessment of pain, ESR, and HAQ). The ACR50 response and ACR70 response are defined respectively, as 50% and 70% improvement. The ACR response is dichotomous: improvement Yes/No. The EULAR response criteria, on the other hand, are based on attained level and change in DAS (van Gestel et al. 1996). They classify a patient as a good, moderate, or non-responder.

In analysis of treatment response in followup studies with repeated measurements, it is preferable also to take intermediate assessments into account. This can be accomplished by plotting the variables over time and calculating the area under the curve (AUC) for each patient in each group (Pham et al. 1999). The mean group AUCs can be statistically compared. An AUC analysis can be performed with a modification of the ACR improvement criteria. The numerical ACR (ACR-N) is determined by the smallest degree of improvement in percentage terms from baseline in three criteria: number of tender joints, number of swollen joints, and the

median of the five remaining measures of disease activity (patient's and physician's global assessment of RA severity, patient's assessment of pain, ESR, and HAQ) (Bathon et al. 2000).

The ultimate goal of anti-rheumatic therapy is that patients achieve a remission in the disease. Improvement of 20% or 50% may retard but not prevent joint damage and functional disability (Pincus et al. 2004). The ACR has proposed a definition for remission which is based on six disease activity variables (four of which are core set variables): duration of morning stiffness not exceeding 15 minutes, no fatigue, no joint pain (by history), no joint tenderness or pain on motion, no soft tissue swelling in joints or tendon sheaths, ESR (Westergren method) < 30mm/h for females and < 20mm/h for males (Pinals et al. 1981). Of these criteria, five or more must be fulfilled for at least 2 consecutive months. The EULAR criteria for remission are DAS28 < 2.6 or DAS < 1.6, neither of which, however, presupposes the absence of inflamed joints (Prevoo et al. 1996). At a DAS cut-off level of 1.6, the percentage of misclassification for patients in remission or not is 10%.

5.8 Economic burden of RA

5.8.1 General

RA imposes a substantial economic burden on society (Pugner at al. 2000, Cooper 2000, Newhall-Perry et al. 2000, Kvien 2004). The total annual costs of RA in Sweden, with a population of 9 million, were estimated in 1994 to be about €350 million (approximately US$430 million) (Jonsson and Husberg 2000). Costs can be divided into direct and indirect (March and Lapsley 2001, Lubeck 2003).

5.8.2 Direct costs

Direct costs are defined as those which are actually paid, e.g., doctor visits, laboratory and x-ray examinations, hospital costs, medication, transportation to the health provider, and special aids. The proportions of various components of costs differ according to health care system and duration of disease. With the exception of patients with recent-onset RA, hospitalization is responsible for the largest component (Guillemin et al. 2004). This situation may, however,

change because some of the new drugs for RA are very expensive. Among the highly dissimilar studies published, RA-related direct costs have been highly skewed with average annual costs ranging from US$2,299 to $8,500 (Lubeck 2003).

5.8.3 Indirect costs

Indirect costs consist of the resources lost (Lubeck 2003). These can be of two kinds. Morbidity costs are mainly the productivity losses of employed patients including reduced earnings and lost tax revenues. Mortality costs are the present value of lost productivity due to premature death caused by disease. In RA, the indirect costs are of major importance, accounting for 50 to 85% of the overall costs of the disease. The main components are sick leave, part-time work, and early retirement. Average indirect costs have ranged from US$1,600 to $27,700 per patient-year, depending on which patients were included and on RA duration (Meenan et al. 1981, Jonsson et al. 1992, Kobelt et al. 1999, Newhall-Perry et al. 2000, Merkesdal et al. 2001, Cooper et al. 2002, Söderlin et al. 2003, Ruof et al. 2003, Hallert et al. 2004). In the early course of RA, indirect costs are already high (Merkesdal et al. 2001, Hallert et al. 2004).

5.8.4 Intangible costs

We can also talk about intangible costs (Lubeck 2003). These represent deterioration in patients' quality of life, as well as that of their families and friends. Leisure and social opportunities are lost, and patients may suffer from disability, pain, and reduced self-esteem and well-being. These costs are extremely difficult to quantify and are often omitted from studies. This aspect of RA outcome can perhaps be assessed better with quality of life instruments (Scott and Garrood 2000, Homik and Suarez-Almazor 2004).

5.9 Loss of work capacity in RA

5.9.1 General

The ability of a person to perform gainful work is a multi-factorial phenomenon dependent on a balance between work requirements and personal characteristics—physiological capacity, psychological characteristics, professional and social skills (Shanahan and Smith 1999), both of which receive different weightings in differing contexts. RA in most cases leads to diminished functional capacity and consequently to diminished work capacity, and often even to total work disability (Yelin et al. 1980, Mäkisara and Mäkisara 1982, Pincus et al. 1984, Mitchell et al. 1988, Yelin 1992, Badley et al. 2001, Sokka 2003b, Backman 2004). However, patients with comparable levels of disease activity and impairment may differ greatly in work capacity, due to the many components of capability to work and the demands of the job. The entire bio-psycho-social field can be mapped by utilizing the International Classification of Functioning, Disability, and Health (ICF).

5.9.2 Definition of ”work disability”

Data on RA-related work disability have featured in a large number of studies. These, however, have been performed with disparate approaches and in discordant settings and contexts (Table 3). First, the demographic and clinical profiles of the patients have differed. Second, some studies have been cross-sectional and others longitudinal. Third, no social security systems of various countries are equivalent. Further, criteria for work disability have not been uniform. Most studies have used pre-term RA-related disability pension or cessation of work due to RA as their indicators of work disability. Not all studies, however, have defined RA or ill health as the cause of the work termination (Fex 1998, Ruof et al. 2003). In addition, many studies have failed to use any external criterion (EC; official database such as a pension register) for work disability measurement, but have relied on patient-reported (PR) information (Table 3), which carries a risk for recall bias.

Permanent work disability represents, however, only a portion of the impact of RA on working capacity. Sick leaves are common, especially in patients with recent-onset RA (Mau et al.

1997). Further, sometimes a patient's work capability recovers even after a long period of work disability, and he or she can return to gainful work. Thus, counting the number of days a patient is work-disabled due to RA during a certain period of time is a more sensitive and appropriate indicator. Work disability days reported by the patient also including sick leaves have been used in a study from Germany and in another from Sweden to estimate loss of productivity in a cohort of patients with early RA over a 3-year and a 1-year followup, respectively (Merkesdal et al. 2001, Hallert et al. 2004). Although RA patients may report their productivity losses adequately, (Merkesdal et al. 2005) data registered by authorities or by an insurance system are preferable, to rule out recall bias. Only one study from Germany has utilized any health-care payer data; it estimated direct and indirect costs for patients with established or late RA (mean disease duration 8.4 years) (Ruof et al 2003).

Table 3. (Next page) Permanent work disability in cross-sectional (CS) and longitudinal (LO) studies on rheumatoid arthritis. Definition of work disability either by patient-report (PR) or by external criterion (EC).

* / ** studies from the same cohort

FIN = Finland, Scand = Scandinavia, S = Sweden, NL = the Netherlands, G = Germany, UK = the United Kingdom, LT = Lithuania, CAN = Canada.

First author	Year published	Country	Type	Years of followup, if stated	N	Disease duration at start/review (years)	Work disabled %	Definition
Yelin	1980	USA	CS	-	180	10	60	PR
Meenan	1981	USA	CS	-	180	9	48	PR
Mäkisara	1982	FIN	CS	-	495	10	50	EC
Pincus	1984	USA	LO	9	75	11/20	85	PR
Yelin	1987	USA	LO	4	306	10; 15; 30	50; 60; 90	PR
Kaarela*	1987	FIN	LO	8	103	<0.5/8	43	EC
Jäntti*	1999	FIN	LO	20	103	<0.5/20	80	EC
Reisine	1989	USA	CS	-	122	NA	43	PR
Borg	1991	Scand	LO	2	83	<2/2	37	EC
Callahan	1992	USA	CS	-	175	11	72	EC
Eberhardt**	1993	S	LO	3	62	<2/3	37	EC
Fex**	1998	S	LO	7	86	<2/7	44	EC
Douglas	1995	NL	CS	-	119	2	55	PR
Reisine	1995	USA	LO	5	392	9/14	44	PR
Allaire	1996	USA	CS	-	469	7	22	PR
Mau	1996	G	LO	6	73	<1/6	49	EC
Fifield	1996	USA	CS	-	501	<3	16	PR
Wolfe	1998	USA	LO	10	456	10	31.5	PR
van Jaarsveld	1998	NL	CS	-	221	2.7	35	PR
Sokka	1999	FIN	LO	9.9	82	<2/2; 9.9	19; 44	EC
Albers	1999	NL	CS	-	76	2.8	51	EC
de Roos	1999	USA	CS	-	960	11.2	27	PR
Barrett	2000	UK	LO	9	160	<0.5/1; 2; 10	23; 33; 39	PR
Chorus	2000	NL	CS	-	720	11.9	33	PR
Merkesdal	2001	G	LO	3	133	<1/2.5	26	EC
Young	2002	UK	LO	5	353	<0.5/5	29	PR
Häkkinen	2003	FIN	LO	2	52	2	31	EC
Hallert	2004	S	LO	1	141	<1/1	12	EC
Dadoniene	2004	LT	CS	-	238	10	48	PR
Lacaille	2004	CAN	CS	-	581	10	27	PR
Verstappen	2005	NL	CS	-	296	4.3	20	PR

5.9.3 Occurrence of permanent work disability

A total of 15 studies on RA-related work disability have been cross-sectional and another 16 longitudinal. Differences in population, setting, study design, disease duration, labor markets, and social security systems are considerable. The proportion of work disabled patients varies greatly (Table 3 and Figure 2), and this variation is larger among cross-sectional studies. Rates are in general higher in European countries than in the USA and Canada (Figure 3). This may be attributable to differences in the social security systems; i.e., welfare facilities are less generous, especially in the USA, than in Europe (Verstappen et al. 2004). Further, the flexibility of the labor market may also influence the work disability rate.

In prospective studies on early RA, the work capacity of RA patients is endangered from the very start of the disease (Borg 1991, Eberhardt 1993, Mau 1996, Sokka 1999, Barrett 2000, Merkesdal 2001, Young 2002, Hallert 2004). Many patients lose their ability to work even during the first year of treatment. Figure 2 illustrates how percentages of permanent work disability at first rise steeply and then subside somewhat in the later course of the disease. The percentages at 20-year and 30-year disease duration are from very old cohorts, and the high numbers may be attributable to less effective drug treatment before the methotrexate era (Pincus et al. 1984, Yelin et al. 1987, Jäntti et al. 1999).

5.9.4 Associations of permanent work disability

Work disability being a bio-psycho-social phenomenon, cessation of working life results from interactions between various physiological variables, social conditions, and work-related factors. Several studies have shown that older age, lower educational level, and longer duration of disease as well as its severity (higher clinical disease activity, lower functional capacity, more extensive structural joint damage), and physically demanding jobs elevate risk for permanent work disability. A review of results of the multivariate regression analyses are in Table 4. Results are parallel in comparing studies on early RA with those with of longer disease duration

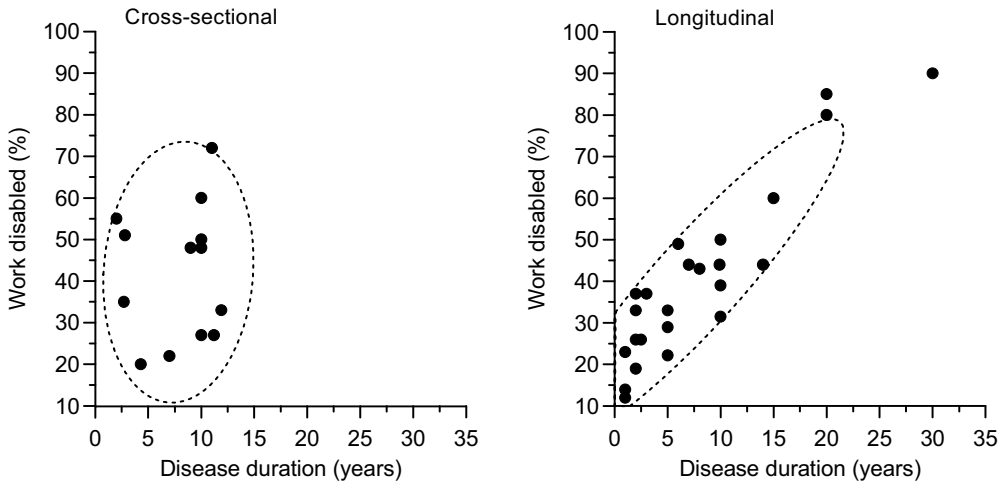

Figure 2. Permanent work disability in the cross-sectional and longitudinal studies in Table 3. Dotted lines: confidence ellipse

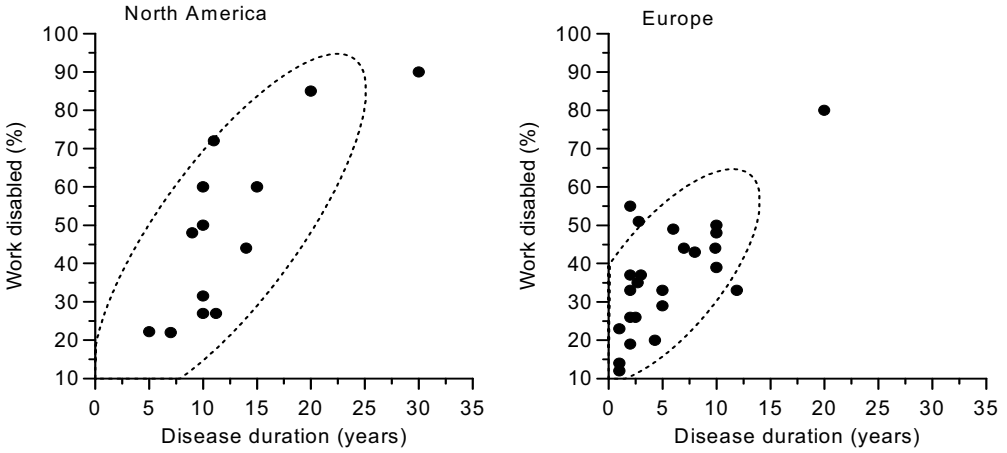

Figure 3. Permanent work disability in the European and North American studies in Table 3. Dotted lines: confidence ellipse

Table 4. Variables associated with RA-related work disability (permanent work disability, with the exception of Hallert). Data from all published studies on work disability since 1987. (+, association found; –, association not found; N/A, non-applicable)

First author	Year published	With Early RA	Long disease-duration	Older age	Less education	Female gender	High ESR	RF-positive	High HAQ score	High joint count	X–ray damage	High pain score	Severe RA	Blue-collar job
Yelin	1987	–	–	+	–	–	–	–	+	+	–	N/A	–	+
Reisine	1989	–	–	+	–	N/A	N/A	N/A	+	N/A	N/A	N/A	+	–
Borg	1991	+	N/A	+	–	–	–	N/A	+	+	N/A	–	N/A	N/A
Callahan	1992	–	–	+	–	–	N/A	–	+	–	–	N/A	N/A	+
Eberhardt	1993	+	N/A	–	–	–	–	N/A	+	–	N/A	–	–	+
Douglas	1995	+	+	–	+	–	+	N/A	+	N/A	N/A	N/A	N/A	N/A
Reisine	1995	–	–	+	–	–	N/A	N/A	N/A	+	N/A	–	N/A	N/A
Mau	1996	+	+	+	N/A	N/A	+	+	+	+	+	N/A	N/A	+
Fex	1998	+	N/A	+	+	–	N/A	N/A	+	–	–	–	N/A	–
Wolfe	1998	–/+	–	–	+	+	+	N/A	+	–	N/A	+	–	+
Sokka	1999	–	N/A	+	–	–	N/A	–	N/A	+	N/A	N/A	N/A	+
Jäntti	1999	–	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	–	N/A	N/A	N/A
de Roos	1999	–	+	+	+	+	N/A	N/A	+	N/A	N/A	+	N/A	–
Barrett	2000	–	N/A	–	N/A	–	N/A	+	+	–	N/A	N/A	N/A	N/A
Holte	2001	–	N/A	+	+	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
Young	2002	+	N/A	+	N/A	+	+	N/A	+	–	+	N/A	N/A	+
Hallert	2004	+	N/A	–	N/A	–	–	–	–	–	N/A	+	N/A	N/A
Lacaille	2004	–	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	N/A	+	N/A	N/A

Functional disability in activities of daily living (high HAQ score) appears to be the best disease-related predictor of permanent work disability (Table 4). On the other hand, evidence that structural joint damage (high x-ray score) predicts work disability is inconsistent. Low formal education level has been associated with work disability in most studies including this variable. Fewer years of schooling often result in a physically demanding occupation. Occupational heavy labor, either self-reported or by job title, has, in most studies in which it has been analyzed, been associated with RA-related permanent work disability.

Evidence is strong that older people with RA have an increased chance of becoming work disabled (Table 4). The elderly tend to have a less favorable course of RA (Kuiper et al. 2001), and aging itself of course has adverse effects on working ability (Wegman 1999, Chan et al. 2000). Performance capacity decreases by age, and long life entails debilitating disorders and diseases. Older people are, on average, less well educated and with less chance of successful vocational rehabilitation, and employers may be reluctant to employ them. Further, it is likely that disability pensions are awarded to them more easily.

Some studies have shown that social- and work-related factors cause a larger impact on permanent work disability than do factors involving RA itself (Yelin et al. 1980, Callahan et al. 1992). For work-related factors other than physical demand, such as job satisfaction, managerial occupation, career opportunities, financial situation, and working hours, evidence is absent or inconsistent for association with work disability (Chorus et al. 2001).

The role of psychological function in the work disablement process has infrequently been examined. Behavioral coping has shown some effect (Chorus et al. 2001).Three prospective studies have found only weak evidence that RA patients with emotional problems are at increased risk for work disability (Borg et al. 1991, Fex et al. 1998, Wolfe and Hawley 1998), and evidence is inconsistent that individuals who experience high pain levels are more likely to be work disabled (Table 4).

Two recent reviews conclude that, in RA, low functional capacity (high HAQ score), physical job demands, older age, and low education level predict permanent work disability (Verstappen et al. 2004, de Croon et al. 2004).

5.9.5 Difficulties in comparison of studies

Caution is needed when reviewing previous research. It is difficult, and may be even misleading, to compare studies with differing settings and approaches (cross-sectional or longitudinal). Comparison is further impeded by disparities in study populations with regard to age, disease severity, and occupational profile, as well as by national differences in social security systems. In addition, treatment strategy has changed profoundly during the last two decades; the older cohorts of RA patients are hardly comparable with recent ones. The occurrence rates for permanent work disability in longitudinal studies in countries with differing insurance systems have, however, been quite parallel (Table 3, Figure 3). Indirect costs (i.e., lost productivity) have dominated RA-related expense everywhere. Relationships of permanent work disability have been rather uniform, although variables analyzed are not the same in all studies (Table 4).

5.9.6 Computation of loss of productivity

Several studies have shown that work absence, by reducing individual earnings and society's productivity, becomes the most expensive outcome of RA (Meenan et al. 1987, Jonsson et al. 1992, Kobelt et al. 1999, Newhall-Perry et al. 2000, Merkesdal et al. 2001, Cooper et al. 2002, Söderlin et al. 2003, Ruof et al. 2003, Hallert et al. 2004). Most estimations of loss of productivity have included only permanent inability to work with only two German studies and one Swedish study including sick leaves, as well (Merkesdal et al. 2001, Ruof et al 2003, Hallert et al. 2004).

Two methods are commonly used for placing a monetary value on lost productivity caused by absence from work. In the human capital approach (HCA), an individual's productivity is valued at its market price (Johannesson 1996): This is the expected or potential gross wage or salary including all employer's contributions, while for self-employed persons, it is the gross personal income including statutory insurance expenses. The HCA is the most widely used method, and this is largely because of its simplicity. Another method, the friction cost approach (FCA), "assumes that someone currently unemployed will replace the disabled worker after a friction period but only if the level of unemployment is above the frictional unemployment" (Koopmanschap and Rutten 1996). The friction period is the time needed to replace a sick

worker, and it is supposed to begin when a worker is first absent. The friction costs include the expenses of hiring, replacing, and training new employees, as well as the lost productivity prior to absent workers being replaced and the decreased productivity output associated with these new employees. To estimate the value of lost productivity by the FCA, the length of friction periods and the friction costs need to be determined at first. Depending on the assumptions employed, the FCA in most cases yields estimates that are lower than the HCA estimates (Lofland et al. 2001). The HCA takes a societal perspective, while the FCA includes employer costs of hiring and training new employees. The validity of the FCA approach has, however, been questioned (Liljas 1998). In any case, estimates of lost productivity depend on data sources and methods used (Verstappen et al. 2005b).

Almost all studies of lost productivity have focused only on days lost from the workplace. Productivity output can also be lost at the workplace because of diminished work performance (Steward et al 2003a). In a recent study on common pain conditions in the US workforce, the majority, about three-fourths, of the lost productive time was explained by reduced performance while at work, a so-called "presenteeism," and not by work absence, "absenteeism" (Steward et al. 2003b). In chronic diseases like RA, presenteeism is likely to be smaller (Wang et al. 2003), but reliable evaluation methods are needed (Lofland et al. 2004). One effort in this field is the WHO Health and Work Performance Questionnaire, a novel instrument for the estimation of absenteeism and presenteeism (Kessler et al. 2003). By using this instrument in analysis of associations between chronic conditions and work performance in a group of reservation agents, customer service representatives, executives, and railroad engineers, those patients with self-reported arthritis/rheumatism reported 8.5 days of excess absenteeism and 15.6 days of excess presenteeism per year (Wang et al. 2003), with results adjusted for age, sex, education, occupation, and other conditions.

In addition to gainful work, unpaid work (household, home maintenance, care-giving, studying) also has societal significance and economic value but is not included in the HCA (Backman et al. 2004).

5.10 Treatment of RA

5.10.1 General

The etiology of RA being unknown, no causal treatment is available. The purpose of treatment of RA is to relieve symptoms and signs of the disease, as well as to prevent permanent tissue damage and its consequences. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used, due to their rapid analgesic effects. The invention of cortisone and its dramatic impact on symptoms of RA led to great enthusiasm in the 1940s, until the hazardous long-term consequences of chronic use of glucocorticoids emerged. Almost all disease-modifying antirheumatic drugs (DMARDs) currently used have been found "by chance," either based on empirical observations or even by theoretical considerations which later have proven incorrect. Testing of the hypothesis that RA is a type of chronic infection led during the last century to the invention of compounds empirically shown to be beneficial in patients with RA: Gold compounds were the first, and later came sulfasalazine and antimalarials. The concept that RA is an autoimmune disease led to testing of immunosuppressive agents. Consequently, azathioprine, methotrexate, and cyclosporine came into clinical use from the 1980s on. Recently, increasing knowledge of mechanisms in the pathogenesis of RA has enabled development of the so-called "biological agents" targeting several cytokines and other mediators of inflammation.

5.10.2 Traditional DMARDS

Ample evidence from randomized clinical trials and observational studies prove that DMARDs can alter the clinical course of RA (Paulus et al. 1990). Treatment responses evaluated by ACR criteria are, however, modest: ACR20 response is observable in 23 to 65%, ACR50 response in 9 to 35%, and ACR70 in 1 to 9% of the patients (Felson et al. 1998), with the highest percentages usually in patients on methotrexate treatment. Remissions, usually transient, occur in about 20% of patients. The effect of the drug is in many cases later lost, and adverse events also may force discontinuation of DMARD. Methotrexate has proven the drug with the most long-term treatment periods (Pincus et al. 1992).

In addition to their reducing disease activity, several studies indicate that early and aggressive therapy with conventional DMARDs improves long-term outcome, including limitation of radiographic damage and better maintenance of physical function (van der Heijde et al. 1996, Munro et al. 1998, Abu-Shakra et al. 1998, Tsakonas et al. 2000, Pincus et al. 2002). Early institution of a DMARD is important; even a delay of treatment by 4 months may be critical (Lard et al. 2001). Most patients, however, benefit insufficiently. To optimize DMARD therapy, the so-called "sawtooth" strategy was proposed in the 1990s (Fries 1990, Fries et al. 1996). It included six principles: early DMARD use, continual serial DMARD use, regular quantitative monitoring of disability to detect insidious progression, setting a disability ceiling for each individual patient, sequential change in DMARD treatment when the ceiling is reached, and deployment of analgesics and NSAIDs as adjunct rather than first-line therapy. With the sawtooth strategy, the remission rate can be increased to about 32% of patients (Möttönen et al. 1996). Radiographic progression has been milder in cohorts enrolled in the 1990s than in earlier cohorts (Sokka et al. 2004). This may reflect more effective drug treatment but can also result from an evolution in the biology of RA toward being milder (Walji and Bykerk 2004).

5.10.3 Role of glucocorticoids

In recent years, data on the potential ability of low-dose corticosteroids to slow radiographic progression in RA have created new interest concerning the optimal use of glucocorticoids (Kirwan 1995, Townsend et Saag 2004). In addition to long-term low-dose strategy, two other approaches have been used: step-down with a high initial dose later tapered off (the COBRA trial; Boers et al. 1997), and bridge therapy aimed at controlling symptoms in the period of high disease activity while awaiting the effect of a newly started DMARD (van Riel et al. 1999). No doubt exists that corticosteroids as a therapeutic adjunct improve suppression of disease activity (Lee et Kavanaugh 2003).

5.10.4 Combination treatment

Some recent studies show that treatment of early RA with combinations of DMARDs is well tolerated and provides a better clinical response than does treatment with a single DMARD.

Not all studies, however, have found any difference in favor of the combination treatment (Maillefert et al. 2003). In the Dutch Combinatietherapie Bij Rheumatoïde Arthritis (COBRA) study on treatment of early RA, an initial step-down combination of high-dose prednisolone, methotrexate, and sulfasalazine for 6 months was compared to monotherapy with sulfasalazine (Boers et al. 1997). Regardless of the subsequent antirheumatic therapy, the combination showed better suppression of the rate of radiological progression which was detectable even after 4- to 5-year followup (Landewe et al. 2002). Economic analysis showed that COBRA therapy added disease control in early RA at a lower or equal cost than did sulfasalazine (Korthals-de Bos et al. 2004).

The FIN-RACo trial group has recently reported the 5-year clinical results of the FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) trial—an open, randomized, followup trial—comparing the efficacy and safety of initial therapy with a combination of DMARDs vs. that of single DMARD in 195 patients with early RA. A total of 178 patients completed the 2-year followup (Möttönen et al. 1999), and of these, 160 (78 in the combination group and 82 in the single group) completed the 5-year extension study (Korpela et al. 2004). At the 2-year visit, about 75% of the patients showed an ACR50 response, and remission was achieved by 40% in the combination-DMARD group and 18% in the single-DMARD group. No significant difference emerged in rate of remissions at 5 years; the corresponding percentages were 28% and 22%. Progression of radiological joint damage, however, was less for patients in the combination group than for those in the single-drug group over the entire followup period: median Larsen radiological damage scores at baseline, 2 years, and 5 years were 0 vs. 2, 4 vs. 12, and 11 vs. 24, respectively.

Calgüneri et al. (1999) compared treatment with a single DMARD (hydroxychloroquine or sulfasalazine or methotrexate), treatment with a combination of methotrexate and hydroxychloroquine or methotrexate and sulfasalazine, and treatment with a combination of all three drugs. The patients on combination therapies improved more than did those on a single DMARD, and the combination of three DMARDs was more effective than the 2-drug combinations. The rates of ACR remission at 2 years were 32%, 45% , and 60% in 1-, 2-, and 3-DMARD groups, respectively.

In the TICORA (tight control for rheumatoid arthritis) study, applying tight followup and continuous intensive treatment with DMARDs and glucocorticoids enabled as high as 65% of patients to fulfill the EULAR remission criteria, which are not as strict as the ACR criteria, however (Grigor et al. 2004).

5.10.5 Biological agents

Recently, biological agents, especially drugs inhibiting function of TNF-α (tumor-necrosis factor α) have been shown to be effective in patients with severe acute or chronic RA. The anti-TNF drugs: infliximab, etanercept, and adalimmumab rapidly neutralize the surplus of the target cytokine, and the treatment response appears during the first 2 weeks. In randomized clinical trials, responses to TNF-α inhibitors have been better than those to conventional DMARD monotherapy (Bathon et al. 2000). Infliximab is recommended to be used with methotrexate (Maini et al. 1998, Lipsky et al. 2000), and a combination of etanercept with methotrexate seems to have an additive effect (Klareskog et al. 2004). The anti-TNF therapies also effectively stop the progression of joint destruction. About 30% of patients, however, do not respond adequately, or the effect is slowly lost. Drawbacks of the biologic agents include a risk for severe infections, especially tuberculosis, and a potential risk for malignancies and for other, at present unsuspected, long-term adverse events (Lee et Kavanaugh 2003). Further, in contrast to the cheap old DMARDs, the new drugs are very expensive.

5.10.6 Impact of treatment on work capacity

Few studies of RA have focused on the impact of patient management on work capacity. Lower risk for work disability was associated with early control of RA in a longitudinal study from the USA (Wolfe et Hawley 1998). A comparison of two historical cohorts from the Norfolk Arthritis Register failed to show improvement in work disability rates (Barrett et al. 2000). In a Finnish cohort starting in the 1990s, patients' functional capacity maintained favorably over a 5-year followup (Häkkinen et al. 2004), although 31% of the patients became permanently work disabled during the first 2 years (Häkkinen et al. 2003).

Only two prospective clinical trials have included work capability as an outcome measure. Borg et al. (1991) studied the effect of early vs. delayed initiation of auranofin on the ability to maintain regular work in a placebo-controlled, double-blind 24-month study of 83 patients with early RA who were gainfully employed at onset. Of these patients, 42 received auranofin 6 mg daily and 41 received placebo. Patients in both groups could be withdrawn from the double-blind drug therapy for insufficient therapeutic effect or for side effects and switched to open DMARD therapy. At the end of this study, 27 patients in the auranofin group were on the trial drug vs.14 in the placebo group. Of the 42 individuals starting auranofin, 23 were still gainfully employed vs. 12 starting with placebo. The respective numbers reporting RA-related cessation of work were 13 and 16. In multivariate analysis of predictors for work disability, treatment group had a slight effect ($P < 0.10$).

In 1999, Yelin et al. (2003) compared the patient-reported employment status of 238 RA patients who had been in clinical trials of etanercept and were currently taking the medication with the status of 259 RA patients in an observational study who had taken no etanercept. All patients had established or late RA with a mean disease duration of 16 years. At diagnosis, 77% of future etanercept users were employed vs. 75% of those who did not take that medication. At the time of the study interview, 71% of the former group and 55% of the latter group were employed. This difference widened to 20 percentage points after adjustments for other variables. On average, the etanercept group worked a mean 7.4 more hours per week in 1999 than did the no-etanercept group.

A non-validated “work productivity” score was included as an outcome in a 52-week double-blind controlled trial comparing the efficacy of leflunomide or methotrexate with placebo (Strand et al. 1999). Of the patients, about 40% had early (<2 years) RA, and the same proportion had late (>5 years) disease. The patients were asked to rank their difficulty with work-related activities due to health problems and health concerns on a 6-point scale (1 = none, 6 = can’t do it). The scores were presented on a 0 to 100 scale with higher scores reflecting higher productivity at home, school, and work. At the end point, significant improvement in work productivity score appeared during treatment with both leflunomide ($P < 0.001$) and methotrexate ($P < 0.05$) compared to placebo. This improvement correlated with ACR responder rates of ≥20% and ≥50%. Functioning and health-related quality of life improved as well.

If effective treatment results in maintenance of patients' work capacity, savings for society can be considerable. So far, only a substudy of the COBRA trial has estimated the economic impact of treatment. In the first 28 weeks, the indirect costs per patient with combined step-down prednisolone, methotrexate, and sulfasalazine compared to sulfasalazine alone were US$2,578 and $3,638, respectively, and the total costs $5,931 and $7,853 (Korthals-de Bos et al. 2004).

5.10.7 Rehabilitation

Rehabilitation, an adjunct of treatment of patients with RA, can be defined as minimizing the consequences of the disease (Straaton et al. 1992, Allaire et al. 1993 and 1996). Planning of rehabilitation can benefit from utilization of the International Classification of Functioning, Disability, and Health (ICF) (WHO 2001). In this scheme, disease consequences are divided into three areas: body functions and structures, activities, and participation. In addition to these, successful rehabilitation requires comprehensive mapping of the patient's entire psycho-social field, i.e., the contextual, personal and environmental, factors in the ICF. The best possible level in each sector is the aim, and this is targeted by multidisciplinary use of rehabilitative treatment modalities: exercise, aids and devices, physical modalities, occupational therapy, patient education, psychological interventions, and vocational rehabilitation. Despite positive clinical experience, scientific evidence as to the effectiveness of rehabilitative interventions is scanty (Vliet Vlieland 2003). In a recent randomized controlled trial, however, vocational rehabilitation had a positive impact on maintenance of work (Allaire et al 2003). The importance of early intervention has been stressed by Marnetoft (2002).

5.11 Finnish social security system

Finland has a statutory national health insurance system. If a resident of Finland, on account of illness, becomes temporarily unable to perform his or her regular job or another similar job, he or she is entitled to a sickness allowance as compensation for lost income. This is payable to persons between ages 16 and 64 and can be awarded to those both employed and self-employed, as well as to those involuntarily unemployed. Self-employment may also take the form of household work or studies. Sickness allowance is paid after completion of a waiting

period comprising the first day of work incapacity and the following 9 weekdays (from Monday through Saturday). This waiting period is, however, waived if incapacity due to the same illness recurs before 30 days have elapsed since the end of the previous payment. Amount of sickness allowance is calculated on the basis of the most recent earnings assessed by tax authorities (for details, see Appendix 1). The allowance is paid for weekdays (including Saturday) for up to 300 days, i.e., for about one year. The claim for sickness allowance must be accompanied by a certificate issued by a doctor or a hospital documenting the claimant's incapacity for work (KELA - the Social Insurance Institution of Finland 2000).

The Social Insurance Institution of Finland is under law required to assess an individual's need for rehabilitation, at the latest, when he or she has received sickness allowance for 60 days. Those whose work and earnings capacity is significantly impaired are entitled to the necessary vocational training or coaching to maintain or enhance their work capacity, and are eligible for a cash benefit called the rehabilitation allowance for the duration of their participation in a rehabilitation program, which means they will be absent from their regular jobs.

If work incapacity persists for at least one year and prevents a person from engaging in gainful employment or from working in his or her own household, he or she can apply for a disability pension. When a claim for this pension is filed, the claimant's work ability is examined on the basis of a doctor's statement by medical examiners. The pension can be permanent or of defined duration. Finland has two complementary pension systems: national pensions linked to residence in Finland and employment pensions linked to past employment. Statutory employment pension insurance covers all employees and self-employed persons.

The Social Insurance Institution is responsible for sickness allowances and national pensions and maintains a register of all benefits awarded. The Central Pension Security Institute maintains a register on employment contracts and employment pensions. Until the year 2004, each Finn above the age of 65 years was entitled to a retirement pension, which could be awarded as a reduced early old-age pension from the age of 60. After that year, the legislation has changed somewhat.

6 AIMS OF THE STUDY

The purpose of the present study was to explore the maintenance of the work capacity of 162 patients with recent-onset, active RA in the Finnish Rheumatoid Arthritis Combination-Therapy Trial (FIN-RACo) cohort; the patients were available for the active workforce at study entry. The following questions were framed:

1) What is the impact of an initial combination-DMARD treatment compared to a single-DMARD strategy on the number of resultant work disability days?

2) What are the baseline predictors of cumulative work disability and productivity loss?

3) What is the impact of treatment response on prognosis for work capacity?

4) What is the monetary value of RA-related loss of productivity caused by days off work, and what are its explanatory factors?

7 PATIENTS AND METHODS

7.1 Selection of patients and study design

From April 1993 to May 1995, 199 patients with recent-onset RA were recruited into the Finnish Rheumatoid Arthritis Combination-Therapy Trial (FIN-RACo) a multicenter, randomized, open parallel-group study designed to compare the efficacy and the tolerability of continuous therapy with a combination of 3 DMARDs and prednisolone with those of single DMARD therapy with or without prednisolone. A total of 18 rheumatology centers and 32 physicians participated. Patient selection criteria were as follows: 1) fulfillment of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for RA (Arnett et al. 1988), 2) age 18 to 65 years, 3) duration of symptoms of <2 years, and 4) active disease with ≥3 swollen joints and at least three of the following: (a) erythrocyte sedimentation rate (ESR) of ≥28 mm/hour or C-reactive protein (CRP) level of >19 mg/liter, (b) morning stiffness of ≥29 minutes, (c) >5 swollen joints, or (d) >10 tender joints.

The following patients were excluded: those who had used DMARDs in the past or had undergone glucocorticoid therapy within the previous 2 weeks; patients with elevated serum creatinine or liver enzymes, with leuko- or thrombocytopenia, with active gastric ulcer, with suspected inability to comply with the protocol, with hypersensitivity to any study medication, or with a history of cancer or heavy use of alcohol; pregnant women or women of childbearing age but not using reliable methods of contraception.

The study was conducted according to the Declaration of Helsinki. The protocol was approved by the national health authorities and by the ethics committees in all 18 participating hospitals. All patients gave their informed written consent. The patients were randomized to receive either combination therapy or a single-DMARD therapy for 2 years. After that the choice of treatment became unrestricted. Randomization was done centrally with sequentially numbered envelopes in blocks of 20, stratified according to rheumatoid-factor status.

The primary objective of treatment in both groups was induction of remission. Patients assigned to the combination-therapy group started with sulfasalazine 500 mg twice daily, methotrexate 7.5 mg/week, hydroxychloroquine 300 mg/day, and prednisolone 5 mg/day. This initial combination, if tolerated, was continued for 3 months. If the clinical improvement at 3 months was under 50% in at least 2 of the 3 criteria (swollen joints, tender joints, and ESR or CRP), the dose of methotrexate was increased to 10 mg weekly and that of prednisolone to 7.5 mg daily. Thereafter, the protocol also included subsequent flexible dose adjustments of sulfasalazine, methotrexate, and prednisolone with remission as a target. The highest dose from 9 months on was 2 g/day for sulfasalazine, 15 mg weekly for methotrexate, 300 mg daily for hydroxychloroquine, and 10 mg daily for prednisolone, as shown in Table 5. On the other hand, if clinical improvement was over 50% at 3 to 12 months, the initial doses were not increased. If the attained 50% response was lost, the doses of DMARDs or prednisolone were increased, or both. If one or several components of the combination had to be discontinued for any reason, a combination of 3 DMARDs was restarted by replacing sulfasalazine and hydroxychloroquine with auranofin (3 to 6 mg daily) and methotrexate with azathioprine (2 mg per kg daily). Other DMARDs could also serve as substitutes. At least 50% improvement had to be achieved at 12 months; otherwise the treatment was defined as a failure, and treatment thereafter became unrestricted.

Table 5. Dosage of DMARDs and prednisolone in the combination-treatment group during the first 36 weeks

	Weeks						
	0-1	2-11	12	16	20	24	36
Methotrexate, mg/week	2.5	7.5	7.5–10	7.5–10	7.5–10	7.5–12.5	7.5–15
Sulfasalazine, g/day	1	1	1	1–1.5	1–2	1–2	1–2
Hydroxychloroquine, g/day	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Prednisolone, mg/day	5	5	5	5–7.5	5–10	2.5–10	0–10

The single-treatment strategy also targeted remission. Patients were treated continuously with one DMARD according to the "sawtooth" principle (Fries 1990). Sulfasalazine (2 g daily) served as the initial drug for all patients, and the dose was increased to 3 g daily at 3 months if clinically indicated. If the clinical response was less than 25% at 6 months or in case of an adverse event, the protocol required that sulfasalazine be replaced with methotrexate (7.5 to 15 mg weekly), which, if tolerated, was given until at least 12 months of followup. Azathioprine could be used as the third DMARD, and further, D-penicillamine, auranofin, injectable gold, or podophyllotoxin sequentially, if treatment response was inadequate or if adverse events occurred. Simultaneous use of prednisolone up to 10 mg daily based on a decision by the treating physician was allowed for patients with continuous active disease. Patients of both treatment arms were allowed to receive intra-articular injections of glucocorticoids as needed; number of injections and amounts of glucocorticoids were recorded.

After 2 years, choice of DMARD and prednisolone treatments became unrestricted. The aim of treatment was still to achieve or maintain remission. Patients in the single-DMARD arm with inadequate response could also be treated with a combination of DMARDs. In the combination-therapy arm, methotrexate could be increased up to 25 mg per week, orally or parenterally, or sulfasalazine up to 3 g daily if clinically indicated and tolerated.

If a patient reached remission during the first year with combination of the initial minimal doses, the drug doses were tapered, and prednisolone, methotrexate, sulfasalazine, and hydroxychloroquine could even be discontinued at 9, 18, 24, and 30 months, respectively (Table 5). For patients who reached remission later and not at the initial doses, prednisolone was the first drug to be tapered off (2.5 mg daily each month) and discontinued. If remission continued, then one DMARD at a time could be discontinued each year by a gradual decrease in its dosage (at first, methotrexate by 2.5 mg every 3 months, then sulfasalazine by 0.5 g every 3 months). Hydroxychloroquine was the last DMARD to be discontinued. If RA reactivated, then the last medication combination with which remission was maintained was reinstituted.

The patients were assessed clinically at baseline and at months 1, 3, 4, 5, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60. In addition to a clinical examination during study visits, safety was monitored by laboratory tests done every 2 weeks from study outset for 3 months, then once a

month until 12 months, and then every second to third month. Tests included complete blood count, serum alanine aminotransferase and alkaline phosphatase activities, creatinine concentration, and urine analysis for blood and protein. Chest radiographs were carried out at baseline and once a year thereafter. If serum enzyme activities exceeded twice the upper limit of normal, the medication dose was lowered, and if the blood white cell count decreased below $3.5x10^9$ per liter or the platelet count below $100x10^9$ per liter, the use of study medication, except prednisolone, was interrupted. All adverse events were documented.

The study was open. Clinical assessments for each patient were made by the same attending rheumatologist in each study center throughout the study, with few exceptions. Disease-activity assessment included the American College of Rheumatology Core Data Set (Felson et al. 1993): count of swollen joints (66 joints examined) and tender joints (68 joints examined); duration of morning stiffness; patient's and physician's global assessment of RA severity on a visual analogue scale (VAS) from 0 (no symptoms) to 100 (most severe disease); patient's assessment of pain on VAS from 0 to 100; patient's assessment of disability by the Stanford Health Assessment Questionnaire (Fries 1980, Hakala et al. 1994a); and ESR and CRP measurements. Radiographs of the hands and the feet were obtained at entry and at 6, 12, 24, 36, 48, and 60 months and scored in sequence by one and the same radiologist (Leena Laasonen) by the method of Larsen (1977). The radiologist was unaware of any patients' treatment and clinical features.

Of the 199 patients eligible and randomized, 4 refused at the start. Of the eventual 195 starting therapy, 97 were assigned to combination therapy and 98 to single-DMARD treatment. After 2 years, the drug treatment strategy became unrestricted, and 51 patients originally randomized to single treatment underwent therapy with a combination of DMARDs (at least two DMARDs simultaneously), and 70 of the 78 RA patients in the original combination group who completed the 5-year followup continued to receive DMARD combinations. All patients in the combination-treatment arm as well as 63 and 62 patients in the single-treatment arm received methotrexate and prednisolone, respectively. The median number of DMARDs taken during the 5-year followup was three both in the original combination group (range 3 to 6) and in the original single group (range 1 to 8). No significant difference in occurrence of adverse events existed between the two groups either during the two first years or during the period between year 2 and year 5.

Response to treatment was evaluated by utilizing the ACR Core Data Set measures and the ACR criteria for improvement in RA (Felson et al. 1993 and 1995). The ACR20 response requires at least a 20% improvement in tender and swollen joint count plus a similar improvement in at least three of the five remaining core measures (patient's and physician's global assessment of the severity of RA, patient's assessment of pain, erythrocyte sedimentation rate, and HAQ). The ACR50 response was defined similarly. The ACR preliminary criteria for remission (Pinals et al. 1981) were modified in such a way that fatigue (a vaguely defined criterion) and duration definition were excluded, and a patient might be on any or no drug treatment. However, a patient in remission had to fulfill all the other five criteria (Table 6).

Table 6. The American College of Rheumatology (ACR) preliminary criteria for remission (Pinals et al. 1981) and the modified criteria used in the present study (FIN-RACo).

	ACR preliminary criteria	FIN-RACo criteria
number of criteria	5 or more	5 (all)
duration	for at least 2 months	0
duration of morning stiffness <15 min	+	+
no fatigue	+	0
no joint pain (by history)	+	+
no joint tenderness or pain when moving	+	+
no soft tissue swelling in joints or tendon sheaths	+	+
ESR: female <30 mm/h, male <20 mm/h	+	+

ESR = erythrocyte sedimentation rate

The measure of overall response (ACR-N) was determined by the smallest degree of improvement in percentage terms from baseline in three criteria: number of tender joints, number of swollen joints, and median of the five remaining measures of disease activity (Bathon et al. 2000).

At the 5-year followup visit, the patients completed—with the assistance of a registered specialist nurse—a questionnaire. Demographic data and duration of formal education were recorded. Employment status since study entry was determined including changes in hours at work, job title, and nature of work. The patients were classified into two groups by job title and by nature of work reported by the patient (physically demanding or physically light work). Further, those with professional/managerial jobs were recorded separately. The patients were asked for permission to access data on their sick leaves and pensions as recorded in the social insurance registers. Patients lost to followup were contacted by letter. For those who could not be contacted or withheld permission, information about sick leave and retirement came based on their informed consent at baseline from case records, including duplicate copies of doctors´ diagnoses and statements as to their possible incapacity for work (Figure 4).

The study population comprised the 162 patients who at baseline were not retired, i.e., were gainfully employed or at least available to the workforce. Demographic and clinical characteristics of these patients at study entry are shown in Table 7.

Table 7. Characteristics of the 162 rheumatoid arthritis patients at baseline

Characteristic	Value
Female, %	62
Age, years, mean ± SD (range)	46 ± 9 (21–64)
Disease duration, months, median (range)	6 (2–24)
Job demands, physically demanding / light	83/79
Rheumatoid factor present, n (%)	116 (72)
ESR, mm/h, mean ± SD	38 ± 23
Number of swollen joints, mean ± SD	14 ± 6
Number of tender joints, mean ± SD	19 ± 9
Physical function (HAQ score), mean ± SD	0.9 ± 0.6
Erosion in hand or foot radiographs, n (%)	81 (53)

SD = standard deviation, ESR = erythrocyte sedimentation rate

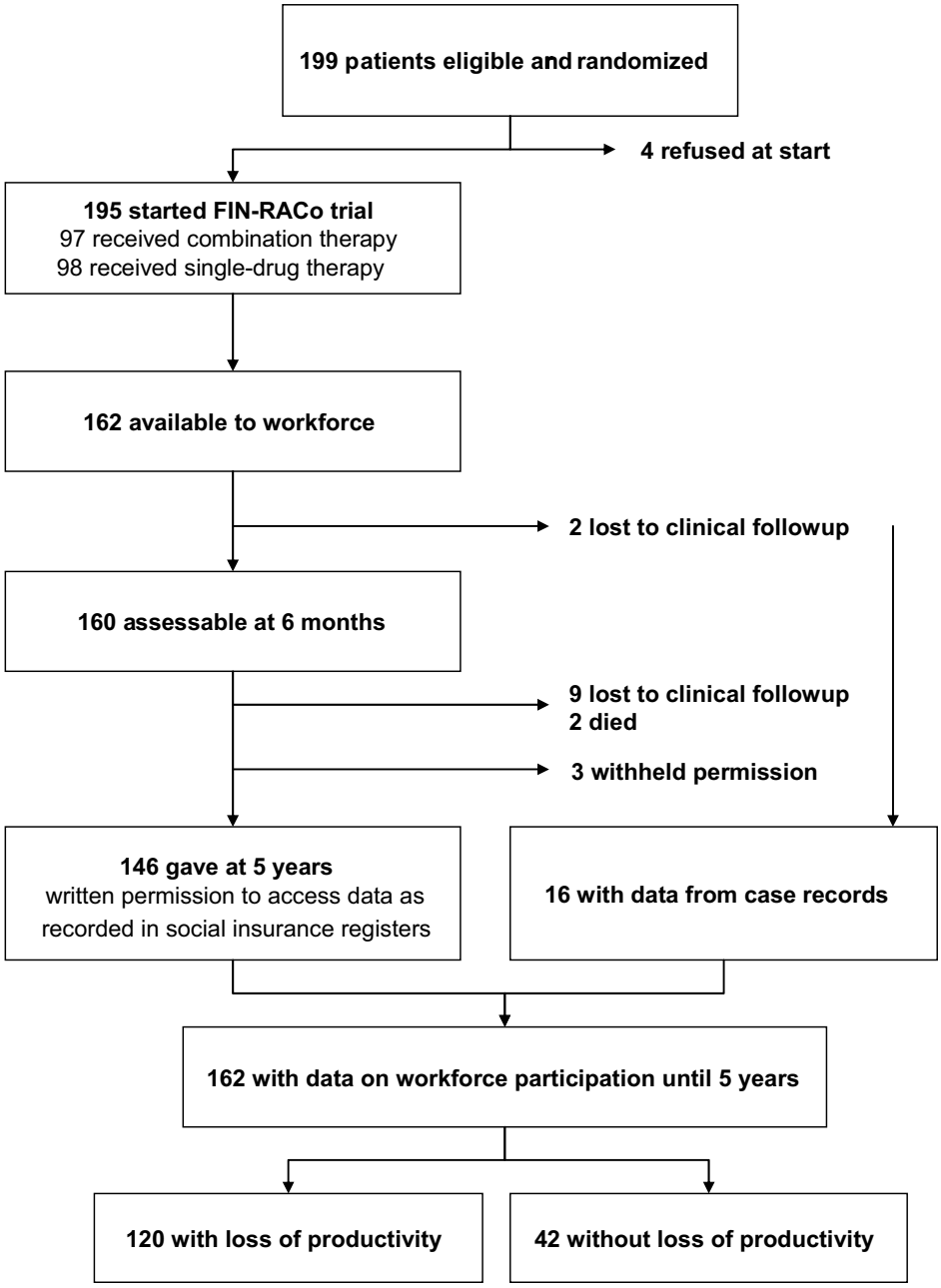

Figure 4. Study flow.

Work disability is defined here as period of time during which a patient was on sick leave receiving a sickness allowance from the Social Insurance Institution, or on a disability pension due to RA. RA was identified in the pension register by code number "714" in the ICD-9 and by "M05" or "M06" in the ICD-10. The sickness allowance register does not contain information on diagnosis codes, which means that the sickness allowances may also be initiated by diseases other than RA. Our patients, however, were followed up strictly according to the study protocol, with all adverse events as well as concomitant diseases documented. The medical records of the 12 patients with severe adverse events, of the 2 patients with sick leave due to a cause other than RA at baseline, and of the 2 patients retired prematurely due to a disease other than RA were reviewed in depth including duplicate copies of doctors' certificates about incapacity to work, and only sick leaves due to RA were included in the analysis.

For each patient, cumulative duration was calculated for sick leaves and RA-related disability pensions. If a person was receiving a part-time (50%) disability pension, the number of days on pension was divided by 2. The number of each patient's work disability days was divided by observation period (years), during which the patient was potentially employable (without taking RA into account). Accordingly, if a patient left the labor market due to retirement on an old-age pension or on a disability pension due to causes other than RA, the date of retirement defined the end of his or her observation period. If a patient was lost to followup or died, the date at which the last data were received for him or her determined the end of the observation. The period of time during which the patients were known to be potentially employable ranged from 0.5 to 5 years.

Our definition of work disability does not cover all "sick days." Very short sick leaves were not registered by the Social Insurance Institution and consequently were not included in our study, because of the minimum period of 10 weekdays (including Saturdays) for sickness allowance. Thus, sick leaves due to most ordinary infections were not included. This minimum period is waived, however, if incapacity due to the same illness recurs before 30 days have elapsed since the end of the previous payment. Consequently, even short sick leaves caused by longer-lasting conditions such as RA were more likely to be included.

The social insurance data contained the sums of allowances and pensions paid as compensation for lost income. The amount of sickness allowance in the Finnish system is calculated on the basis of the preceding year's earnings assessed by the tax authorities. Based on the allowance paid over the first sick leave period, the income before contracting RA can be calculated by applying the formula backwards. For the patients with case record data on days off work but without data on benefits paid, the income of each job was that recorded by Statistics Finland (www.stat.fi).

For estimation of lost productivity, the human capital approach (HCA) (Johannesson 1996) was applied: a person's productivity was valued at the market price. An employee's productivity was defined as equaling the total costs to an employer (salary plus supplementary social welfare expenses), and a self-employed person's productivity as equaling his or her personal income plus the statutory health and pension insurance expenses. Productivity after the first year was computed based on annual income indices of each branch of the economy from Statistics Finland with addition of the supplementary expenses (a statutory percentage of income) in every year (Appendix 2); these sums were converted to prices in 2002 by the general index of wages and salaries. For each patient, mean productivity per day over the 5-year followup was calculated and multiplied by cumulative number of days off work to yield loss of productivity. For a person receiving a disability pension for part-time (50%) work, number of days on pension was divided by 2. Euros were converted to US dollars at the January 2004 exchange rate (1 euro = $1.22).

7.2 Linking of items of HAQ to ICF categories

The items of HAQ (section 5.7.7) at 6 months were linked to activity limitations of the ICF (section 5.7.11, Table 2). The linking principles of Cieza et al. (2002) were applied with a two-level classification procedure. The HAQ yielded three ICF categories: "mobility," "self-care," and "domestic life." The category "mobility" was divided into three subcategories: "changing and maintaining body position;" "carrying, moving and handling objects;" and "walking and moving plus moving using transportation" (Table 2). Each (sub)category comprised at least two items (questions) of the HAQ questionnaire yielding 0 to 3 points, and the highest number of points separately in each of them defined the function score of a patient.

7.3 Statistical analyses

Results are expressed as means with standard deviation (SD) and 95% confidence intervals (95% CI), and as medians with interquartile range (IQR). Confidence intervals for the means of work disability benefits (Study III) and for the means of cost of lost productivity (Study IV) were obtained by bias-corrected and accelerated bootstrapping (5,000 replications) (Efron et Tibshirani 1980), because of the skewed distribution of the variables. Normality of variables was evaluated by Shapiro-Wilk statistics.

Statistical comparison between treatment groups (Study I) was made by Mann-Whitney test and by Hodges-Lehmann estimation of the shift of medians. Median regression, also known as least absolute value models, served to estimate adjusted medians. In Study III, patients were divided into four groups according to clinical treatment response at 6 months with the ACR criteria as boundary lines: remission, ACR50 improvement with some symptoms, ACR20 improvement but less than ACR50, and less than ACR20 improvement. Statistical comparisons between response groups were made by Kruskal-Wallis test with Monte Carlo P-value and by permutation one-way ANOVA with general scores. The global test for differences was followed by pair-wise multiple comparisons by the Dwass-Steel-Chritchlow-Flinger method (Hollander and Wolfe 1999). In Study IV, statistical comparisons between the groups (quartiles of AUC of ACR-N and four groups for increase in number of erosions) were made by chi-square test as well as permutation test and ANOVA with general scores, both with Monte Carlo P-values.

Retirement analysis (Study I) was based on product-limit estimation; Mantell-Cox test served to identify any differences. A Cox proportional hazards regression model with robust estimate of variance was used to estimate adjusted risks for retirement.

In Study II, a continuation-ratio logistic model for ordinal response data was applied (Fienberg 1980); the forward stepwise method was used in multivariate analysis of predictors of work disability days. The patients were divided into four categories according to cumulative duration of work incapacity per patient-observation year: 1) 0 days (N = 41), 2) 1 to 19 days (38), 3) 20 to 149 days (42), and 4) 150 to 365 days (41). Linearity of trend was analyzed by Cuzick's 1985 test. Patient's and physician's global assessments (scale 0 to 100) were dichotomized at

50 (median rounded to the nearest tenth). The self-reported function (HAQ score) was dichotomized at 1.0. The Cox proportional hazards model with robust estimate of variance served to analyze the predictors of permanent RA-related disability pensions. In Study IV, a multiple imputation (Markov-chain Monte Carlo) method was applied to fill in missing values of individual HAQ questions. A continuation-ratio model for ordinal outcomes served for analysis of relationships of loss of productivity to other variables. Associations are summarized as odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (95% CI).

8 RESULTS

8.1 General

Of the 162 patients available for the workforce at baseline, 80 were randomized to receive combination therapy (COMBI) for 2 years, while 82 were randomized to single-DMARD therapy (SINGLE). At baseline, 82% of the patients in the SINGLE group and 89% of those in the COMBI group were gainfully employed; one patient in each group worked part-time. Equal numbers of patients in the two groups were on sick leave because of RA: 25 (30%) in the SINGLE and 25 (31%) in the COMBI group. In addition, two patients in the SINGLE group were on sick leave due to reasons other than RA. An imbalance existed in the number of unemployed job-seekers at entry: 10 patients in the SINGLE arm (12%) vs. 4 (5%) in the COMBI arm. This imbalance leveled off, however, during followup, and a total of 18 and 14 patients, respectively, were for some period unemployed; median duration of unemployment was 13 months in the SINGLE and 14 in the COMBI arm. One person in each group was in vocational training at study entry. In addition, at baseline, four patients in each group were doing housework, none of whom, however, housewives in the traditional sense; all had completed professional training, and with the exception of three, all did paid work for at least some time during the course of the study.

During the followup, 10 patients in each group changed employment, and equal proportions experienced a change in their working conditions (12 patients in the SINGLE and 11 in the COMBI). Five patients in the SINGLE group and two patients in the COMBI retired due to age. For two other patients in the COMBI, the reason for pre-term retirement was a non-rheumatic disease (myeloma, coronary heart disease). Two patients in the SINGLE group died during the study, one from myelodysplastic syndrome, the other from alcohol intoxication.

At 5 years, we had data on the labor-force participation of 158 patients. We failed to contact four patients randomized to the SINGLE group who had discontinued followup. Five (6%) were unemployed in each study group. Three patients in the SINGLE arm and one in the COMBI arm were doing housework, and the same number were employed part-time outside

the home. Of the 162 patients, 146 gave their written permission to obtain social register data. For the remaining 16 (11 in SINGLE, 5 in COMBI) data about sick leave and retirement was obtained, based on their informed consent given at baseline, only from case records. Treatment groups were comparable with regard to most demographic and clinical variables (Table 8). More women, however, were in the SINGLE group (p = 0.11).

Table 8. Characteristics of patients available for the workforce in the combination-drug (COMBI) and single-drug (SINGLE) groups at study entry.

Characteristic	Treatment group	
	COMBI (n=80)	SINGLE (n=82)
Demographic:		
Female/Male	45/35	56/26
Married, %	73	77
Age, years, mean ± SD	45 ± 9	46 ± 10
Duration of education, years, mean ± SD	11 ± 4	11 ± 3
Job title, physically demanding / light	41/39	42/40
Professional/managerial job, n (%)	18 (23)	14 (17)
Disease duration, months, median (range)	6 (2–22)	7 (2–24)
Rheumatoid factor present, n (%)	59 (74)	57 (70)
Measures of disease activity:		
ESR, mm/h, mean ± SD	37 ± 24	38 ± 20
Number of swollen joints, mean ± SD	14 ± 6	14 ± 7
Number of tender joints, mean ± SD	18 ± 8	20 ± 10
HAQ score, mean ± SD	0.8 ± 0.6	0.9 ± 0.6
Radiographic:		
Number with radiographs available	77	79
Larsen score, median (IQR)	2 (0–4)	2 (0–7)
Erosion in hand or foot radiographs, n (%)	39 (51)	43 (54)

SD = standard deviation, ESR = erythrocyte sedimentation rate, HAQ = the Stanford Health Assessment Questionnaire, IQR = interquartile range.

8.2 Work disability days (Study I)

Work disability days accumulated at almost steady, but differing rates in each treatment arm for the entire followup period (Figure 5). No deviation occurred in the SINGLE arm after 2 years, although drug treatment became unrestricted at that time. In 5 years, the median cumulative duration of work disability per patient-observation year was 32 (IQR 6–293) days in the SINGLE group and 12 (0–54) days in the COMBI group (P = 0.008); the sex- and age-adjusted medians were 37 (95% CI 24–50) and 18 (95% CI 5–31) (P = 0.009). Mean duration of work disability per patient-observation year was 128 days for the SINGLE group and 78 days for the COMBI. The superiority of the combination treatment was primarily related to difference in cumulative duration of sick leaves—i.e., work disability with a maximal length of 300 weekdays—between the groups: the median number of days on sick allowance per patient-observation year was 30 (IQR 6–68) in the SINGLE group and 12 (IQR 0–44) in the COMBI (P = 0.002). The respective means were 48 and 23 days.

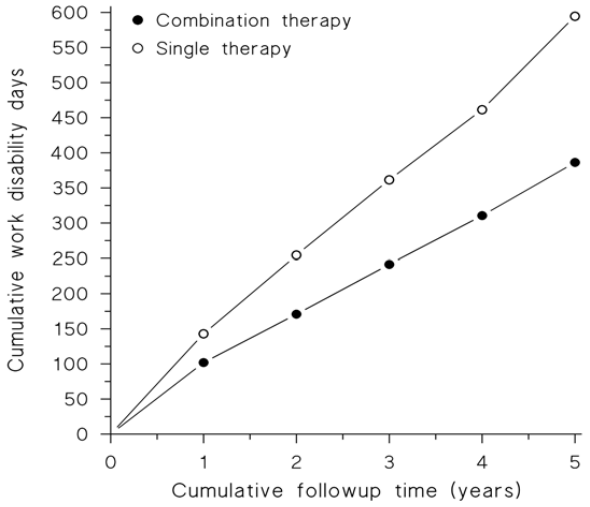

Figure 5. Accumulation of work disability days for patients who initially received a single DMARD or a combination of DMARDs. (Reprint from Arthritis & Rheumatism, Vol 50, Puolakka K, et al., Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: A five-year randomized followup trial, pp. 55-62, 2004, with permission from John Wiley & Sons, Inc.)

8.3 Work disability benefits (I)

The median of the work disability benefits, i.e., the sum of sick allowances and RA-related disability pensions paid by the social insurance system per patient-observation year, was US$1,094 (IQR 121–8,409) for the SINGLE group and $372 (IQR 0–1,973) for the COMBI (P = 0.008, sex and age-adjusted P = 0.009). Mean benefits were $4,404 and $2,534. The overall difference between the groups during the 5 years was a total of $569,740.

8.4 Loss of productivity (IV)

As Figure 6 illustrates, 120 of the 162 (101 female, 61 male) patients experienced days off work causing loss of productivity over the 5-year followup; females more often (83; 82%) than males (37; 61%); P = 0.002.

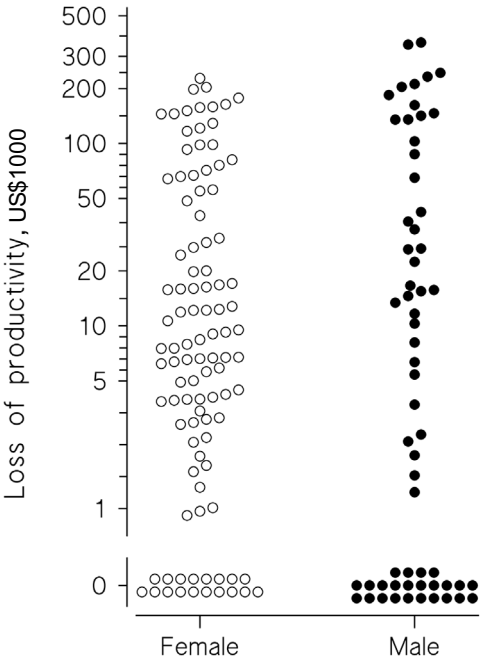

Figure 6. Loss of productivity over the 5-year followup for the 162 patients with early RA.

Over the 5-year followup, estimated mean loss in productivity was $40,501 (95% CI 31,187–52,587). It was $8,805 (95% CI 6,784–11,160) per patient-observation year, for women $7,902 (95% CI 5,927–10,414) and for men $10,300 (95% CI 6,575–15,736). Mean age-and sex-adjusted loss of productivity per year was $10,260 (95% CI 7,338–13,865) in the SINGLE group and $7,313 (95% CI 4,826–10,539) in the COMBI group; the difference was $-2,947 (95% CI -7,279–1,331, P = 0.17).

Loss of productivity was estimated on the basis of personal income before contracting RA. This was calculated by the register data for 101 patients. For the remaining 19, incomes came from Statistics Finland. To test the validity of the statistical income data, we compared the calculated incomes of the 101 patients to annual incomes in their jobs according to Statistics Finland; difference between the means was -$574 (95% confidence interval -3,073–1,113), i.e., showing no significant difference. The income data of the 19 patients can thus be regarded as valid. Personal income before contracting RA had no predictive value for loss of productivity.

Figure 7 shows loss of productivity per patient-year in each year of followup. In the first year, the loss was highest and was mostly (89%) because of sick leave (~work disability up to one year). After that, permanent work disability dominated progressively: 79%, 89%, 92%, and 94% in the second, third, fourth, and fifth year, respectively. Total annual loss began to increase slowly after the second year.

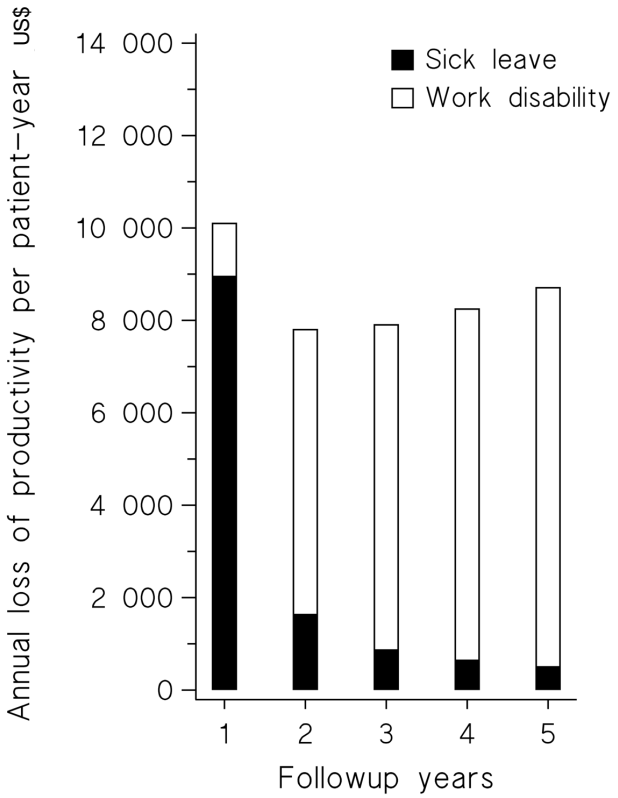

Figure 7. Loss of productivity because of sick leave and permanent work disability in each year of followup

8.5 RA-related permanent work disability (I)

In most cases, continuous work disability for over one year translated into a permanent dropping out of working life, but two patients receiving SINGLE therapy and one receiving COMBI therapy could resume working after about 2 years of followup. After 3 years, this was possible for only two patients originally randomized to the SINGLE treatment. During the 5-year followup, 24 (30%) patients in the SINGLE arm and 16 (20%) patients in the COMBI arm retired on a permanent disability pension due to RA; one of them in the SINGLE group was working part-time. No significant difference, however, was found in those pensions; the product-limit estimator of the rate of pensions was 30% (95% CI 20–40) for the SINGLE and 20% (95% CI 11–29) for the COMBI arm (P = 0.16). A considerable proportion of our patients, 18 (22%) in the SINGLE and 11 (14%) in the COMBI group, were continuously and eventually permanently unable to work right from the first month of followup.

8.6 Gainfully employed patients (I)

Most studies on RA-related work disability have included only patients gainfully employed. To facilitate comparison, we analyzed this subset of our patients separately, i.e., we excluded patients who at baseline were unemployed, were doing household work, or were in vocational training. At baseline, 67 patients receiving SINGLE therapy (82% of the non-retired) and 71 receiving COMBI therapy (89%) were employed gainfully. In this population, the median cumulative duration of sex- and age-adjusted work disability per patient-observation year was 29 days (95% CI 18–39) in the SINGLE and 15 (95% CI 5–24) in the COMBI group (P = 0.03). When those who were gainfully employed at baseline (N = 138) were compared to the rest of the patients (N = 24), no significant difference appeared in work disability days per patient-observation year (median: 19 vs. 57 days; p = 0.25), in job type (50% vs. 58% had a physically demanding occupation; P = 0.45), or in length of formal education (mean: 11 vs. 12 years; P = 0.23).

8.7 Predictors of cumulative work disability (II)

In univariate analysis, the initial combination treatment was protective against extension of work disability. On the other hand, risk factors were older age, low education level (<10 years of schooling), and high score (≥50) in patient's and in physician's global assessments of RA severity, tender-joint count, ESR, and self-reported disability (HAQ score ≥1.0). Physically demanding job did not quite reach statistical significance as a risk factor.

In the forward stepwise multivariate model, patient's and physician's global assessments, HAQ, low education level, and age remained significant risk factors; the initial combination therapy was still protective. A linear trend was observable between work disability categories and patient's global (P = 0.001) or physician's global assessment (P <0.001), especially in the single-treatment arm.

8.8 Predictors of permanent RA-related disability pension (II)

In univariate analysis, older age, low education level, patient's and physician's global assessments ≥50, and HAQ disability (score ≥1.0) were significant predictors. However, in multivariate analysis, only patient's global assessment, HAQ, and age remained significant.

8.9 Impact of early treatment response on maintenance of work capacity (III)

The 159 patients assessed at 6 months were divided into groups according to their ACR response. Of these, 29 (18%) were in the clinical remission (group I), 66 (42%) attained an ACR50 response but not remission (group II), 29 (18%) achieved an ACR20 response but not an ACR50 (group III), whereas the response for 35 (22%) patients was less than the ACR20 (group IV). These groups also differed in some other characteristics: Patients in group III had the most active RA at baseline, while those in group IV had the longest sick leave during the initial 6 months. Those patients in remission at 6 months (group I) used considerable sick leave during the first 6 months, but after that, their number of work disability days was minimal (Figure 8). The 6-month improvement was a surrogate of the remaining disease activity at that moment: For all activity variables except ESR, a monotonous trend appeared across response groups. The Larsen score was lowest in the remission group.

A distinct monotonous trend appeared between the four response groups and cumulative duration of work disability per patient-observation year from 6 through 60 months of followup; medians (IQR) of work disability days were 0 (0–3), 4 (0–131), 16 (0–170), and 352 (16–365) in groups I, II, III, and IV ($P < 0.001$). Pair-wise multiple comparisons showed a significant difference between all groups except the ACR50 (II) and the ACR20 (III) groups ($P = 0.71$).

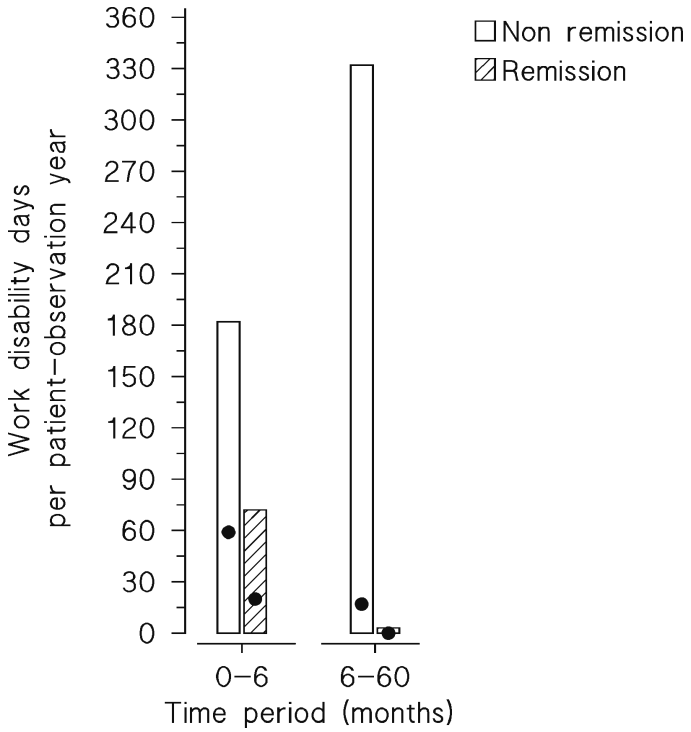

Figure 8. Work disability days during the first 6 months and thereafter by 6 month treatment response. Median (●) with IQR.

From 6 through 60 months of followup, the social insurance system paid a total of US$533,600 in work disability benefits. The mean cumulative benefit per patient-observation year was $3,355 (95% CI 2,514–4,198). A patient with a poor 6-month treatment response (in group IV) cost Finland's social insurance system US$7,226 per year more (95% CI 5,124–9,272) than did a patient in remission (Figure 9). The difference across the four response groups was significant (P <0.001).

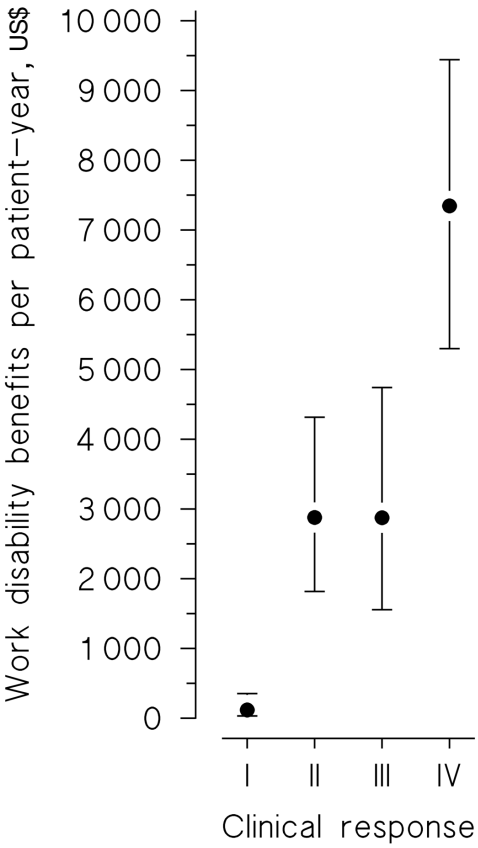

Figure 9. Annual work disability benefits during 6 to 60 months by 6-month response group. I = remission, II = ACR50 but not remission, III = ACR20 but not ACR50, IV = no ACR20. Means (●) with 95% CI.

None of the 29 patients in remission (I) at 6 months became permanently work disabled as a result of RA during the 5-year followup, whereas 19 (54%) did so in the group without an ACR20 response (IV). If a patient was not in remission at 6 months, risk for permanent work disability was no better in the ACR50 (II) than in the ACR20 group (III): 23% vs. 21% of the patients in the respective groups ended with a permanent RA-related disability pension. Figure 10 illustrates the age-, sex-, job type-, and education level-adjusted rates of RA-related permanent work disability in the four response groups. At 12 months, 30 patients were in remission; each of these had achieved at least an ACR50 response at 6 months. Over the 5-year followup, none of the 44 patients in remission either at 6 months or at 12 months ended with RA-related permanent work disability.

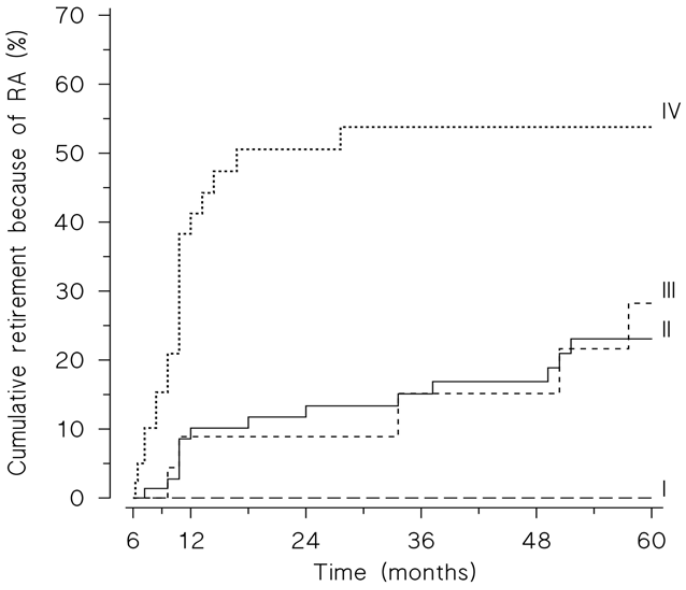

Figure 10. Rate of permanent RA-related disability pensions by 6-month treatment response. Groups: I = remission, II = ACR50 with some symptoms, III = ACR20 but not ACR50, IV = no ACR20. Age-, sex-, job-, education level-adjusted. (Reprint from Arthritis & Rheumatism, Vol 52, Puolakka K, et al., Early suppression of disease activity is essential for maintenance of working capacity in patients with recent-onset rheumatoid arthritis: Five-year experience from the FIN-RACo trial, pp. 36-41, 2005, with permission from John Wiley & Sons, Inc.).

8.10 Association with loss of productivity (IV)

Loss of productivity (section 8.4) was prominently associated with patients´ clinical improvement over the 5-year followup. When the patients were divided into groups according to quartiles of area under the curve (AUC) of the ACR-N measure, the inverse correlation with improvement was distinct: Age- and sex-adjusted mean loss of productivity per patient-year was US$1,343 (95% CI 394–2,630) and $18,242 (95% CI 13,008–24,219) for the highest (best) and lowest (worst) quartiles of AUC in ARC-N improvement, respectively (P <0.001 for

difference across groups). Loss of productivity was also related to increase in number of radiological erosions of the hands and feet, although less strongly (P = 0.045 for difference across the groups of 0, 1 to 4, 5 to 9, and ≥10 erosions).

At 6 months, the mean HAQ score was 0.30 (SD 0.39) for women and 0.24 (SD 0.36) for men. The HAQ at 6 months was linked to the ICF to explore what kind of activity limitations were the best predictors of loss of productivity. The HAQ yielded three ICF categories, of which "mobility" was further divided into three subcategories (Table 2). Even a minimal increase in HAQ score or slightly diminished performance in any of these five categories and subcategories of the ICF was associated with loss of productivity in univariate analysis (Figure 11). For multivariate analysis, the patients were divided into four groups according to the annual monetary value of lost productivity: 0 (N = 41), $1 to1,200 (N=38), $1,201 to 10,000 (N=42), and over $10,000 (N=41). HAQ score >0 led to elevated odds entering a higher cost-group in ordered logit models (age- and sex -adjusted odds ratio [OR] 5.4, 95% CI 3.0–10.8; P <0.001), but in a separate multivariate model, of the five ICF (sub)categories, only disability (score >0) in "changing and maintaining body position" led to increased odds (OR 4.4, 95% CI 1.6–12.2; P = 0.005). Age was a risk factor, as well (OR 1.1, 95% CI 1.0–1.1; P <0.001).

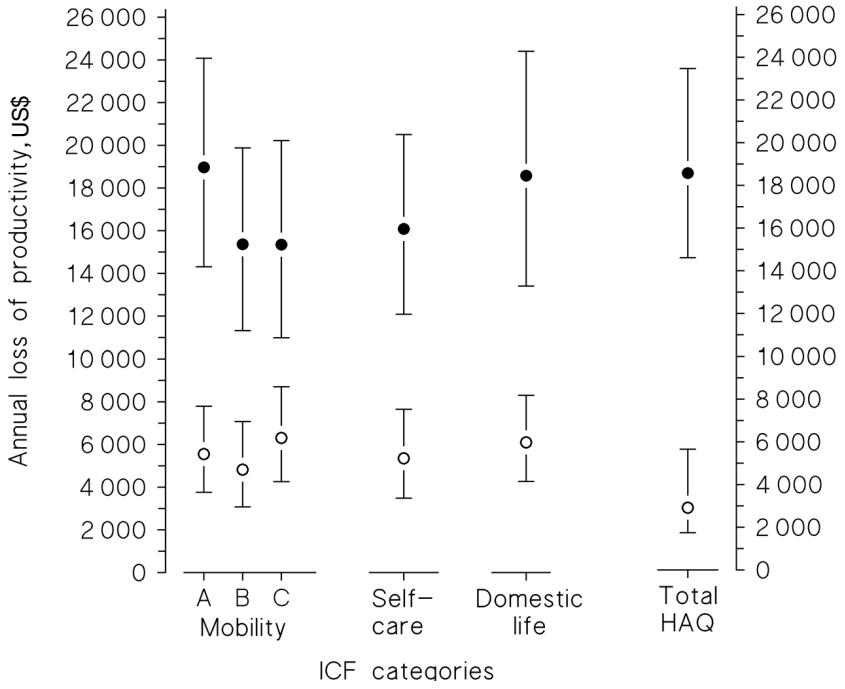

Figure 11. Loss of productivity per patient-year over a 5-year followup by 6-month disability: total Stanford Health Assessment Questionnaire (HAQ) score and separate items of HAQ linked to categories of the International Classification of Functioning, Disability, and Health (ICF). Means (○ patients with score 0, ● patients with score >0) with 95% confidence intervals. Subcategories of mobility category: A = changing and maintaining body position; B = carrying, moving, and handling objects; C = walking and moving plus moving using transportation.

9 DISCUSSION

9.1 Monetary value of loss of productivity

In this study, we could estimate with greater accuracy than before the monetary value of lost productivity in early RA by utilizing official register data on RA-related work disability days and on individual incomes as assessed by the tax authorities. Productivity losses because of sick leaves and because of RA-related disability pensions were estimated separately over the 5-year followup, whereas almost all previous studies have included only permanent work disability. The loss of productivity caused by days off work was considerable, on average US$8,805 per patient-year.

The two longitudinal studies, which also included sick leaves, had patient-reported days off work as an outcome and based their estimation of loss of productivity on the gross income of all gainfully employed people in a country (Merkesdal et al. 2001, Hallert et al. 2004). The average annual loss in the German study (Merkesdal et al. 2001), US$11,750 (SD 1,120), was somewhat higher than in ours ($8,805; 95% CI 6,784–11,160). An explanation may be disparities in therapy: half our patients initially received treatment with a combination of DMARDs, and our rate of permanent work disability was lower (25% in 5 years vs. 26% in 3 years), despite our cohort's including more active RA cases and fewer white-collar workers. The first year's loss of productivity in the Swedish study (Hallert et al. 2004), US$10,646 (SD 16,503) (1 euro = US$1.22), is comparable to our mean of $10,150. The Swedish patients had less active RA at baseline, and only 70% of them received DMARDs one year after inclusion, compared to 100% of our patients. Further, incomes differ between countries.

Patient-reported data on sickness absence carry a risk for recall bias, and the mean income of the population may not be valid information as to the patients' actual wages and salaries. In another German study, which utilized health-care payer's data on medical costs and on sickness absence, mean annual sick leave costs of the gainfully employed patients were US$3,459, and mean annual work disability costs of the retired patients were $10,197 (1 euro = US$1.22) (Ruof et al. 2003). That study, however, was cross-sectional, and the patients had

established or late RA with mean disease duration of 8.4 years. Further, RA-related and other work disability could not be distinguished and the productivity costs did not include contributions by employers to social insurance.

Our study had accurate data about RA-related days off work over time allowing estimation of time-related changes in loss of productivity. The loss was already substantial during the early course of the disease, as also estimated earlier (Merkesdal et al. 2001, Hallert et al. 2004); lost productivity was actually highest during the first year of followup and then was almost entirely attributable to days off work because of sick leave. From the first year on, risk for permanent work disability was high, as well. This parallels to others' results (Borg et al. 1991, Eberhardt et al. 1993, Mau et al. 1996), although a wider comparison to studies done with less exact methods, with different approaches and settings, with populations differing with regard to age, disease severity, and occupational profile, and in countries with differing social security systems may not be very fruitful.

We sought to secure the validity of our material against the shortcoming in social insurance data that the registers included no causes of sick leaves, by reviewing the case reports of patients with a probability of longer-term sick leave due to causes other than RA. According to Finnish legislation, short sick leaves due, for instance, to ordinary infections were not included, but short sick leaves caused by longer-lasting conditions such as RA were more likely to be included. More than two-thirds of the work disability days were because of disability pensions, the causes of which were confirmed by the code of the main diagnosis. Further, the majority of sick leave days were linked to these RA-related pensions. We had no social insurance register data for 16 patients. Until the end of followup, however, they regularly visited a study center at least every 6 months, and we could obtain data on their sick leaves and pensions from case records including duplicate copies of doctors´ statements with diagnoses. In short, it is most likely that nearly all RA-related work disability days were included in our analyses, with hardly any sickness-absence days included caused by other conditions. In calculation of lost productivity, we had to use income data from Statistics Finland for 19 patients. Comparison of the job-specific income from these statistics with individual incomes calculated on the basis of register data showed that the income data from statistics are valid.

In the Finnish social security system, in addition to those gainfully employed, those doing household work are also entitled to work disability benefits; the same is true for students and for those involuntarily unemployed. As all these groups could become work disabled and receive work disability benefits, we chose to include them in our study. Further, none of the eight patients doing housework at baseline was a housewife in the traditional sense; all of them had completed professional training, and five were at least for some period gainfully employed during the 5-year followup. On the whole, the dynamics of working life caused both an influx into and an outflow from the labor force as well as changes in working conditions. A total of 20 (12%) patients of the 162 changed employment, and a further 23 (14%) experienced a change in their working conditions during the study. Part-time work has not been very common in the Finnish labor market, and only four individuals were employed part-time at 5 years. Earlier, Yelin et al. (1987) have reported the work dynamics of a retrospective cohort of RA patients with mean disease duration of 11 years. From the year of diagnosis, 19% of their patients changed jobs and a further 20% experienced a change in their working conditions.

Of our patients, 32 (20%) were for some period unemployed over the 5-year followup, but only the days off gainful work were, by definition, included in calculation of loss of productivity. Work disability days and lost productivity of individual patients were in the analysis proportioned according to the period of time a patient was known to be available to the workforce. This patient observation period ended before 5 years for seven patients because of retirement due to age, for two because of pre-term retirement due to non-rheumatic disease, and finally for two because of death. A further nine patients were for other reasons lost to followup.

Controversy prevails as to how to value what is known as the opportunity costs for individuals. We chose the most widely used method, the human capital approach (HCA), which estimates loss of productivity as a function of an individual's wage or salary (Johannesson 1996, Koopmanschap and Rutten 1996) and thus the HCA allocates a zero euro figure to the opportunity costs of individuals who are not paid for work outside of the home, such as people working in their own household and students.

Our estimation of RA-related loss in work productivity was limited to days missed from the workplace. A disease, however, can cause reduced productivity at work, as well. This

"presenteeism" (Stewart et al. 2003a) was not estimated here, which obviously means underestimation of the indirect costs of RA in this study. In a recent study of lost productivity time due to common pain conditions in the US workforce, most of the pain-related lost productivity time occurred while employees were at work and was in the form of reduced performance (Stewart et al. 2003b). The estimated presenteeism was greater than the absenteeism (work absence) for self-reported arthritis/rheumatism, as well (Wang et al. 2003).

9.2 Impact of early aggressive treatment with a combination of DMARDs on work capacity

Our hypothesis was that aggressive initial treatment, i.e., the combination of three DMARDs and prednisolone which had induced more remissions at 2 years (Möttönen et al. 1999), could reduce work disability days more than did the traditional "saw-tooth" treatment strategy with a single DMARD at a time. This turned out to be true, and this was the first time a study clearly showed the impact of a drug treatment for RA on patients' ability to work. The between-group difference was most distinct for number of days on sick leave; the rates for permanent RA-related disability pensions actually did not differ significantly between treatment arms. Initial treatment with a combination of DMARDs was, in multivariate analysis, the only protective baseline factor against work disability days. The number of adverse events in the COMBI arm was no higher than in the SINGLE arm (Möttönen et al. 1999, Korpela et al. 2004). The ACR responses achieved by the FIN-RACo combination treatment at 2 years were among the best ever reported with DMARD therapy. Actually, the percentage of improvement with each very expensive biologic agent has not been better, although comparison of differing studies may be misleading. The FIN-RACo trial was planned to compare the two treatment strategies; the study design does not allow comparison of the impact of individual DMARDs on maintenance of working capacity.

Despite the significant difference in work disability days in favor of the combination-treatment strategy, no significant difference existed between the SINGLE and COMBI groups in the monetary value of lost productivity. The broader distribution of this variable compared to days off work is the likely explanation: Variation in days is multiplied by variation in income.

Accumulation of work disability days was almost linear in both treatment arms over the entire 5-year followup, and the absolute difference between arms increased steadily over time. It is remarkable that no deviation from the linear progression in cumulative days of work disability occurred in the SINGLE arm after 2 years, when treatment strategy became non-restricted, and those patients randomized to single treatment who had not responded adequately to the saw-tooth strategy were switched to a combination of DMARDs and prednisolone. Our results lend further support to the concept of "window of opportunity" in the early course of RA (O'Dell 2002).

In 1977, Luukkainen et al. had already shown that with gold, earlier treatment gives better results than its later initiation. The FIN-RACo Trial Group has demonstrated that if start of therapy with DMARDs is delayed, the frequency of remissions at 2 years is lower with single-DMARD therapy but remains the same with COMBI therapy, when both are compared to earlier treatment (Möttönen et al. 2002). Early institution of a combination of DMARDs is important, as well, based on the positive effect of initial therapy with a combination of DMARDs on retardation of radiological progression at 2 years which continued at least up to 5 years, despite liberation of therapy in both treatment arms after 2 years (Korpela et al. 2004). The COBRA Group has similar findings: An initial 6-month cycle of intensive combination therapy including high-dose glucocorticoids has resulted in sustained suppression of radiographic joint damage independent of subsequent therapy (Landewe et al. 2002).

To explore the work dynamics of patients with RA and to increase the number of patients in our cohort, we also included patients who at baseline were not gainfully employed. However, when only gainfully employed patients were analyzed, the difference in favor of the combination-treatment arm was maintained; the smaller P value is likely to be due to the smaller sample size.

The FIN-RACo Trial was a randomized but open study. The protocol of the work disability project was not, however, presented to the Trial Group until 1998, when the first patients had been followed up for almost 5 years. Consequently, at least in the early years of followup, which according to our results were decisive for prognosis, it was very unlikely that the clinicians would have dealt differently with work disability assessment in the treatment arms. Further, all decisions concerning longer sickness allowances and disability pensions were made

by a neutral external examiner in the Social Insurance Institution or in the pension insurance companies.

9.3 Risk factors for diminished work capacity

Older age and fewer years of schooling appeared as risks factors for diminished work capacity, as in almost all studies (Table 4). The only significant disease-related predictors of work disability days were the HAQ and the global assessments of RA severity by patient and by physician at baseline. Thus, the questionnaire measures of the ACR Core Data Set were far better predictors than were measures of inflammation and joint damage. This parallels to the results of Pincus et al. (2003), who found that an index of the three core data set patient questionnaire measures distinguishes the efficacy of active treatment from that of placebo as effectively as the American College of Rheumatology 20% response criteria do. Both the HAQ and patient's global assessment are a type of sum variable which also reflect the patient's psychological constitution (Smedstad et al. 1997, Wolfe 2000), supporting the bio-psycho-social concept of working ability and work disability.

The HAQ has appeared in studies as a predictor of work disability almost invariably (Table 4). This is in accordance with the finding that the early HAQ predicts future functional capacity (Leigh et Fries 1992). In early RA, like that of our patients at entry, HAQ scores are correlated with disease activity, and the usually low radiographic scores have little influence (Scott et al. 2000). Pain has been the most important individual determinant of the HAQ at least in established or late RA (Sokka et al. 2000), but much of the variation remains unexplained and may be influenced by psychosocial factors (Wolfe 2000).

Global assessments of RA severity have been included in work disability studies infrequently (Callahan et al. 1992, Wolfe et Hawley 1998, Sokka et al. 1999), although these variables are sensitive to change in clinical trials and are predictors of future disability (Wolfe and Cathey 1991, Buchbinder et al. 1995). Patients' global assessment correlates independently with pain and depression (Smedstad et al. 1997). Baseline psychological measures were not assessed in the present study, and, in fact, few studies have included them, none having found any of them to be independent predictors of work disability (de Croon et al. 2004).

In most studies in which this has been analyzed, RA-related permanent work disability has been associated with occupational heavy labor (Table 4). Here, however, a physically demanding job was not a significant risk factor, at least in part because of the crude measure of physical work demand: the job title. Other studies, however, have not used any better indicator of actual work load. Such a measure is obviously needed both for future studies and for the everyday clinic, because workplace and job characteristics evidently have an influence on one's ability to continue working. Occupational evaluation should start promptly after diagnosis of RA in order to discover any need for adaptations (Gignac et al. 2004, Allaire 2004). Vocational rehabilitation had a positive impact on maintaining a career in a recent US randomized controlled trial (Allaire et al 2003). Another report from the USA indicated, however, that the state-federal vocational system was underutilized (Straaton et al. 1996). The situation may be the same in Finland.

The predictors of work disability can be serve as "red flags" warning the clinician of an ominous prognosis for the patient's work capacity and of a risk for high societal costs. This may aid in choice of treatment strategies and in guiding a patient at risk into vocational rehabilitation before any loss of employment.

9.4 Impact of treatment response on maintenance of work capacity

One of our most important findings is that early treatment response appeared to be a strong predictor of future work capacity. Earlier, one-year followup variables have appeared as more accurate predictors of 5-year disability than were baseline variables (Wiles et al. 2000). Further, ACR20 and ACR50 responder rates at one year of followup correlate with "work productivity" score in a study comparing leflunomide and methotrexate with placebo (Strand et al. 1999). In the present study, the induction of remission by 6 or 12 months translated into maintenance of work capacity over the entire 5-year followup. The situation was almost the opposite for patients without at least an ACR20 response at 6 months: more than half of them ended with a permanent RA-related disability pension. The RA-related pre-term retirement occurred early in the course of disease, 65% of cases during the first year of followup. Similar results have been reported elsewhere (Borg et al. 1991, Eberhardt et al. 1993, Mau et al. 1996). It was a surprise that the patients without remission at 6 months had a similar prognosis in

terms of working ability irrespective of achieving the ACR20 or the ACR50 response, which, however, significantly separated the patients with regard to remaining disease activity. In this respect, no safe range existed for disease activity at 6 months. This emphasizes remission as the ultimate goal of treatment and is parallel to the finding that improvement of 20% or 50% may retard but not prevent joint damage and functional disability (Pincus et al. 2004).

We found the trend expected between treatment response and duration of sick leave over the preceding 6 months. Prolonged sick leave may impose injurious psychosocial consequences that also partly account for the risk for future work disability. This also underscores the importance of early aggressive treatment and prompt initiation of vocational rehabilitation when needed.

The ACR response criteria include HAQ score. The 6-month HAQ alone was associated with loss of productivity over 5 years, and even a minimal HAQ disability (score >0) raised the odds of entering a higher cost group. Previously, the HAQ score at one year of followup was the best predictor of HAQ disability at 5 years (Wiles et al. 2000). In the present study, of the items of HAQ at 6 months, only diminished performance in the ICF subcategory "changing and maintaining body position" (Table 2) was independently associated with higher loss of productivity. Thus, with regard to work capacity, the explanatory powers of the items of HAQ diverge. On the other hand, the ICF offers a useful conceptual framework for addressing various aspects of capability to work as well as activities of daily living and should be increasingly applied in clinical rheumatology.

The favorable impact of successful treatment was further indicated by the distinct relationship of RA improvement over time (AUC of ACR-N) to savings in lost productivity. Progression of radiological damage of joints in hands and feet was associated with lost productivity, as well.

These results point out the importance of early and aggressive RA treatment. However, from the present point of view, the initial "aggressive" combination treatment in the FIN-RACo trial was not very vigorous, at least in the first months of followup. The highest methotrexate dose during the first 2 years was 15 mg per week, and this dose was not allowed until 9 months onwards. In addition, despite remission as a target of the treatment in both groups, the protocol

regarded the ACR50 response to be sufficient in some situations: If clinical improvement at 3 to 12 months was over 50%, doses were not increased. This is probably why the peak in remissions (N = 54) was not achieved until 2 years (Möttönen et al. 1999, Korpela et al. 2004). Further, the initial single treatment with sulfasalazine was continued at least up to 12 months if improvement at 6 months was ≥25%, and only if response was less did sulfasalazine have to be switched to methotrexate. Accordingly, the decisive 6-month response was entirely related to efficacy of sulfasalazine in the single arm. After 2 years, a switch from single-DMARD therapy to treatment with a combination of DMARDs was allowed, as well as an increase in methotrexate dose up to 25 mg per week. Instituting of a more intensive treatment was, however, too late in most cases: only two patients could resume work capacity after 3 years. If long-term remission was induced, the FIN-RACo protocol included reducing of drug doses, but this resulted in relapses in many cases.

A trial that compares a combination of DMARDs with step-up therapy in only those patients who need step-up therapy remains yet to be done. However, because of the good results and favorable security profile of the FIN-RACo combination, we can recommend it as a standard initial medication in recent-onset active RA. The methotrexate dose can be increased early to 25 mg per week orally or subcutaneously and sulfasalazine to 3 g daily. The results of the TICORA study (Grigor et al. 2004) suggest that the FIN-RACo combination with a more rapid increase in drug dosage could have induced more remissions. Another question is, should patients have induction therapy with glucocorticoids or with TNF inhibitors (O'Dell 2004 and 2005)? In a recent small study, 20 patients with early (<12 months) RA treated with methotrexate (MTX) were randomized to receive either infliximab or placebo for 12 months (Quinn et al. 2005) and were followed up for another 12 months. At one year, 78% and 67% of the MTX-plus-infliximab-treated patients fulfilled the ACR 50 and ACR70 response criteria, respectively, versus 40% and 30% of the MTX-plus-placebo-treated patients. Response was sustained in 70% of the MTX-plus-infliximab-treated patients at one year after cessation of induction therapy. Between-group differences according to the HAQ and RA Quality of Life questionnaires were maintained ($P < 0.05$), although differences in DAS28, ACR response, or radiographic scores were not. Working ability was not assessed as an outcome. Obviously, larger studies are needed on biologic drugs as an adjunct to a single DMARD or to a combination of DMARDs, preferably studies including cost-effectiveness analysis as well.

9.5 Socio- and pharmaco-economic implications

In the present study, the mean monetary value of one year's work absence was US$36,000. This means that if a young person loses his or her working ability forever, the societal cost in a lifetime can rise to hundreds of thousands of dollars. Inducing an early remission thus will result in substantial savings. Not only days at the workplace are lost or saved, however. Disease-related reduced performance while at work can also result in considerable productivity losses (Steward et al. 2003a and 2003b), but such presenteeism was not assessable here. The economic scope is even more extensive, if we consider the value of unpaid work, not to mention quality of life.

We did not calculate or compare our patients' direct medical costs, because most were determined by the study protocol. In any case, cost of drug treatment with conventional DMARDs can be regarded as very reasonable. This is in contrast to the very expensive biological agents, none of which were used for any of our patients during the 5-year followup period. Of the anti-TNF agents, infliximab in combination with methotrexate, and etanercept alone have been more efficacious than is methotrexate alone in treatment of patients with early RA (Bathon et al. 2000, St Clair et al. 2004, Quinn et al. 2005). Addition of methotrexate to etanercept improves its efficacy further (Klareskog et al. 2004). No comparison of the biological drugs with combinations of DMARDs, however, exists. In a longitudinal study of patients with both early and established RA, longer-term treatment with etanercept resulted in increased hours of employment (Yelin et al. 2003), but more research in the form of well-designed randomized controlled trials should include work capacity as an outcome (Lacaille 2005).

An important question is: Can more remissions be induced in early RA by adding a biological agent to a combination of DMARDs and prednisolone? Further, can induction treatment of defined duration yield longer-term benefit? Treating all recent-onset RA with biologicals for years seems economically untenable for society, at least at present, but we have no means to select those patients who will not respond adequately to conventional DMARDs and thus will benefit most from biologicals. Another burning question is: What is the best policy to treat patients on combination-DMARD therapy not in remission at 6 months? Our results suggest that more vigorous therapy should be instituted, at least for patients of working age. Is a TNF

inhibitor the best option? In any case, even expensive therapy actually lowers cost to society, if a patient's working ability can be maintained. Consequently, at least if working ability is in danger, institution of an anti-TNF agent might be prudent.

9.6 Can the results be generalized?

Can our findings be generalized and offer a prescription for our colleagues who are treating patients with RA? Our results come from a study of patients with recent-onset, active RA which compares two treatment strategies for their RA, treating them with a single DMARD or with a combination. Strictly speaking, the difference observed in work disability days refers only to the patients treated according to the protocol of this multi-center trial. Our cohort is representative, within its selection criteria, for Finnish patients with early active RA, because, for social insurance reasons, practically all new RA patients in Finland are referred to rheumatologists in outpatient clinics of the public hospitals, and the participating centers covered almost every region of the country. Between-country differences in patient profiles in terms of occupational and psychosocial variables of course may exist. Further, the social security system may have some influence on sick leave and work disability; rates of permanent RA-related work disability have been in general higher in European countries than in the USA (Table 3), where welfare facilities are more limited than in Europe. In addition, the flexibility of the labor force market may affect the work disability rate, and the monetary value of lost productivity is dependent on income level. Within these restrictions, our results may be generalized to patients with early RA.

10 CONCLUSIONS

This project was a prospective cohort substudy of the Finnish Rheumatoid Arthritis Combination-Therapy (FIN-RACo) Trial, a randomized clinical trial conducted from 1993 to 2000. A total of 162 patients with recent-onset rheumatoid arthritis (RA), aged 18 to 65 and available to the workforce, were followed up for 5 years. The aims of the study were achieved, and the questions framed were answered as follows.

10.1 Answers to the questions

10.1.1 Impact of initial drug treatment strategy on work disability

Aggressive initial treatment with a combination of DMARDs for 2 years led to statistically significantly better working ability and fewer days off work over the entire 5-year followup than did therapy with a single DMARD. In the single-drug arm, no deviation in the accumulation of work disability days occurred after 2 years; this provides support to the concept of window of opportunity during the early course of RA.

Our results indicate that the impact of RA on work capacity should be measured, instead of mere recording of permanent work disability, by a count of the days that patients are unable to work.

10.1.2 Baseline predictors of cumulative work disability and productivity loss

The only RA-related baseline variables predicting productivity loss were the global assessments of RA severity by patient and physician and the Stanford Health Assessment Questionnaire (HAQ). These questionnaire measures are simple and easy to use routinely in clinical practice, and high scores should be regarded as alarm signals for poor outcome, more lost work days, and high costs to society.

Implementation of the International Classification of Functioning, Disability, and Health (ICF) provides new insight into the assessment of functional capacity, as well as into the mapping of workplace characteristics and other environmental and personal factors which may impact on capability to work. This can aid in choice of patients at risk for vocational rehabilitation before their loss of employment.

10.1.3 Impact of treatment response on prognosis for work capacity

The prognosis for a patient's working ability was distinctly impacted by early treatment response. Remission during the first year translated into maintenance of work capacity whereas even an ACR50 response at 6 months was often inadequate to prevent permanent work disability and high costs to society. Further, failure to achieve an ACR20 response carried a very high risk for permanent work disability.

10.1.4 Monetary value of RA-related loss of productivity

During the 5-year followup, of 162 patients, 120 (75%) used sick leave or experienced longer-term work disability or both, which led to lost productivity; these were women more often (82%) than men (61%) (P = 0.002). During the first year, the loss of productive time was highest, resulting mainly from sick leave (89%); thereafter, permanent work disability dominated.

The monetary value of the work absence-related lost productivity estimated by the human capital approach was substantial, on average US$8,805 per patient-observation year (95% confidence interval 6,784–11,160), although all patients received remission-targeted DMARD therapy, and half underwent aggressive initial treatment with a combination of DMADRs. Rheumatoid arthritis is truly an expensive disease.

10.2 Clinical implications

In conclusion, the impact of RA on work capacity should be estimated by calculating days off work. Evaluating RA-related reduced work performance while in the workplace with valid

instruments will further broaden the concept of lost productivity in future. To minimize the substantial risk of productivity loss, all patients with active, recent-onset RA should be treated aggressively from the very start, with the target being early remission. ACR20 or ACR50 responses are not satisfactory to prevent work disability. If remission is not achieved by 6 months, more vigorous therapy should be instituted. The role of the expensive biological drugs in early RA needs more research. However, even an expensive drug may result in cost-savings to society if it maintains a patient's working ability, as the average loss from one year's work disability in our study was US$36,000.

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12 REFERENCES

Abu-Shakra M, Toker R, Flusser D, Flusser G, Friger M, Sukenik S, Buskila D. Clinical and radiographic outcomes of rheumatoid arthritis patients not treated with disease-modifying drugs. Arthritis Rheum 1998;41:1190-5.

Aho K, Heliövaara M, Sievers K, Maatela J, Isomäki H. Clinical arthritis associated with positive radiological and serological findings in Finnish adults. Rheumatol Int. 1989;9:7-11.

Aho K, Kaipiainen-Seppänen O, Heliövaara M, Klaukka T. Epidemiology of rheumatoid arthritis in Finland. Semin Arthritis Rheum 1998:27:325-334.

Aho K, Heliövaara M. Risk factors for rheumatoid arthritis. Ann Med. 2004;36:242-51.

Albers JM, Kuiper HH, van Riel PL, Prevoo ML, van't Hof MA, van Gestel AM, Severens JL. Socio-economic consequences of rheumatoid arthritis in the first years of the disease. Rheumatology (Oxford) 1999;38:423-430.

Allaire SH, Partridge AJ, Andrews HF, Liang MH. Management of work disability. Arthritis Rheum 1993;36:1663-1670.

Allaire SH, Anderson JJ, Meenan RF. Reducing work disability associated with rheumatoid arthritis: identification of additional risk factors and persons likely to benefit from intervention. Arthritis Care Res 1996;9:349-357.

Allaire SH. Update on work disability in rheumatic diseases. Curr Opin Rheumatol 2001;13:93-98.

Allaire SH, Li W, LaValley MP. Reduction of job loss in persons with rheumatic diseases receiving vocational rehabilitation. A randomized controlled trial. Arthritis Rheum 2003;48:3212-18.

Allaire SH. What work changes do people with arthritis make to preserve employment, and are such changes effective? Arthritis Rheum 2004;51:871-873.

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger TA Jr, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL, Hunder GG. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.

Backman CL, Kennedy SM, Chalmers A, Singer J. Participation in paid and unpaid work by adults with rheumatoid arthritis. J Rheumatol 2004;31:47-56.

Backman CL. Employment and work disability in rheumatoid arthritis. Curr Opin Rheumatol 2004;16:148-152.

Badley EM, Wang PP. The contribution of arthritis and arthritis disability to nonparticipation in the labor force: a Canadian example. J Rheumatol 2001;28:1077-1082.

Barrett E, Scott D, Wiles N, Symmons D. The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. Rheumatology 2000;39:1403-9.

Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Finck BK. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-1593.

Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A, van der Linden S. Randomized comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-318.

Borg G, Allander E, Berg E, Brodin U, From A, Trang L. Auranofin treatment in early rheumatoid arthritis may postpone early retirement. Results from a 2-year double blind trial. J Rheumatol 1991;18:1015-20.

Brekke M, Hjortdahl P, Kvien TK. Self-efficacy and health status in rheumatoid arthritis: a two-year longitudinal observational study. Rheumatology (Oxford) 2001;40:387-392.

Bruce B, Fries J. The Stanford health assessment questionnaire: dimensions and practical applications. Health Qual Life Outcom 2003:1:20.

Buchbinder R, Bombardier C, Yeung M, Tugwell P. Which outcome measures should be used in rheumatoid arthritis clinical trials? Clinical and quality-of-life measures' responsiveness to treatment in a randomized controlled trial. Arthritis Rheum 1995;38:1568-80.

Calgüneri M, Pay S, Caliskaner Z, Apras S, Kiraz S, Ertenli I, Cobankar V. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol 1999;17:699-704.

Callahan LF, Bloch DA, Pincus T. Identification of work disability in rheumatoid arthritis: physical, radiographic, and laboratory variables do not add explanatory power to demographic and functional variables. J Clin Epidemiol 1992;45:127-138.

Carty SM, Snowden N, Silman AJ. Should infection still be considered as the most likely triggering factor for rheumatoid arthritis. J Rheumatol 2003;30:425-429.

Chan G, Tan V, Koh D. Ageing and fitness to work. Occup Med (Oxford) 2000;50:483-91.

Chorus AMJ, Miedema HS, Wevers CWJ, van der Linden S. Labour force participation among patients with rheumatoid arthritis. Ann Rheum Dis 2000;59:549-554.

Chorus AMJ, Miedema HS, Wevers CWJ, van der Linden S. Work factors and behavioural coping in relation to withdrawal from the labour force in patients with rheumatoid arthritis. Ann Rheum Dis 2001;60:1025-32.

Cieza A, Brockow T, Ewert T, Amman E, Kollerits B, Chatterji S, Ustun TB, Stucki G. Linking health-status measurements to the international classification of functioning, disability and health. J Rehabil Med. 2002;34:205-210.

Cieza A, Stucki G. New approaches to understanding the impact of musculoskeletal conditions. Best Pract Res Clin Rheumatol 2004;18:141-154.

Combe B, Cantagrel A, Goupille P, Bozonnat MC, Sibilia J, Eliaou JF, Meyer O, Sany J, Dubois A, Daures JP, Dougados M. Predicitive factors of 5-year health assessment questionnaire disability in early rheumatoid arthritis. J Rheumatol 2003;30:2344-2349.

Conaghan PG, Green MJ, Emery P. Established rheumatoid arthritis. Best Pract Res Clin Rheumatol 1999;13:561-575.

Cooper NJ. Economic burden of rheumatoid arthritis: a systematic review. Rheumatology (Oxford) 2000;39:28-33.

Cooper NJ, Mugford M, Symmons DPM, Barrett EM, Scott DGI. Total costs and predictors of costs in individuals with early inflammatory polyarthritis: a community-based prospective study. Rheumatology (Oxford) 2002;41:767-774.

de Croon EM, Sluiter JK, Nijssen TF, Dijkmans BA, Lankhorst GJ, Frings-Dresen MH. Predictive factors of work disability in rheumatoid arthritis: A systematic literature review. Ann Rheum Dis 2004;63:1362-1367.

Cuzick J. A Wilcoxon-type test for trend. Statistics Med 1985;4:87-89.

Dadoniene J, Stropuviene S, Venalis A, Boonen A. High work disability rate among rheumatoid arthritis patients in Lithuania. Arthritis Rheum 2004:51:433-439.

Doeglas D, Suurmeijer T, Krol B, Sanderman R, van Leeuwen MA, van Rijswijk MH. Work disability in early rheumatoid arthritis. Ann Rheum Dis 1995;54:455-60.

Eberhardt K, Larssin BM, Nived K. Early rheumatoid arthritis: some social, economical, and psychological aspects. Scand J Rheumatol 1993;22:119-123.

Efron B, Tibshirani R. An Introduction to the Bootstrap. New York: Chapman and Hall; 1993.

Escalante A, del Rincón I. How much disability in rheumatoid arthritis is explained by rheumatoid arthritis. Arthritis Rheum 1999;42:1712-1721.

Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, Furst D, Goldsmith C, Kieszak S, Lightfoot R, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36:729-740.

Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R Jr, Paulus H, Strand V, Tugwell P, Weinblatt M, Williams HJ, Wolfe F, Kieszak S. The American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.

Felson DT, Anderson JJ, Lange ML, Wells G, LaValley MP. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? Arthritis Rheum 1998;41:1564-1570.

Fex E, Larsson B, Nived K, Eberhardt K. Effect of rheumatoid arthritis on work status and social and leisure time activities in patients followed 8 years from onset. J Rheumatol 1998;25:44-50.

Fienberg S. The Analysis of Cross-Classified Categorical Data. 2nd edition ed. Cambrigde, MA: MIT Press; 1980.

Fifield J, Reisine S, Sheehan TJ, McQuillan J. Gender, paid work, and symptoms of emotional distress in rheumatoid arthritis. Arthritis Rheum 1996;39:427-435.

Firestein GS. Rheumatoid synovitis and pannus. In: Hochberg MC et al., ed. Rheumatology. St Louis: Mosby; 2003:855-884.

Frank RG, Beck NC, Parker JC, Kashani JH, Elliott TR, Haut AE, Smith E, Atwood C, Brownlee-Duffeck M, Kay DR. Depression in rheumatoid arthritis. J Rheumatol 1988;15:920-925.

Fries J, Spitz P, Kraines R, Holman H. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137-145.

Fries J. Reevaluating the therapeutic approach to rheumatoid arthritis: the "sawtooth" strategy. J Rheumatol 1990;22 Suppl:12-15.

Fries J, Williams CA, Morfield D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. Arthritis Rheum 1996;39:616-622.

van Gestel AM, Prevoo MLL, van't Hof MA, van Rijswijk MH, van de Putte LBA, van Riel PLCM. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum 1996;39:34-40.

van Gestel AM, Stucki G. Evaluation of established rheumatoid arthritis. Best Pract Res Clin Rheumatol 1999;13:629-644.

Gignac MA, Badley EM, Lacaille D, Cott CC, Adam P, Anis AH. Managing arthritis and employment: making arthritis-related work changes as a means of adaptation. Arthritis Rheum 2004;51:909-916.

Green MJ, Deodrah AA. Bone changes in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2001;15:105-123.

Griffith J, Carr A. What is the impact of early rheumatoid arthritis on the individual? Best Pract Res Clin Rheumatol 2001;15:77-90.

Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomized controlled trial. Lancet 2004;364:263-269.

Gordon DA, Hastings DE. Clinical features of rheumatoid arthritis. In: Hochberg MC et al., ed. Rheumatology. St Louis: Mosby; 2003:765-780.

Guillemin F. Functional disability and quality-of-life assessment in clinical practice. Rheumatology (Oxford) 2000;39(suppl. 1):17-23.

Guillemin F. How to assess musculoskeletal conditions. Assessment of disease activity. Best Pract Res Clin Rheumatol. 2003 Jun;17:415-26.

Guillemin F, Durieux S, Daures JP, Lafuma A, Saraux A, Sibilia J, Bourgeois P, Sany J. Costs of rheumatoid arthritis in France: a multicenter study of 1109 patients managed by hospital-based rheumatologists. J Rheumatol 2004;31:1297-1304.

Hakala M, Nieminen P, Manelius J. Joint impairment is strongly correlated with disability measured by self-reported questionnaires. Functional status assessment on individuals with rheumatoid arthritis in a population based series. J Rheumatol 1994;21:64-69 (a).

Hakala M, Nieminen P, Koivisto O. More evidence from a community based series of better outcome in rheumatoid arthritis. Data on the effect of multidisciplinary care on the retention of functional ability. J Rheumatol 1994;21:1432-1437 (b).

Hakala M, Nieminen P. Functional status assessment of physical impairment in a community based population with rheumatoid arthritis: severely incapacitated patients are rare. J Rheumatol 1996:23:617-623.

Hallert E, Thyberg I, Hassa 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.

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 (Oxford) 2004;43:1374-1382.

Harrison BJ, Symmons DPM, Brennan P, Bankhead CR, Barrett EM, Scott DGI, Silman AJ. Inflammatory polyarthritis in the community is not a benign disease: prediciting functional disability one year after presentation. J Rheumatol 1996;23:1326-1331.

van der Heide A, Jacobs JWG, van Albada-Kuipers GA, Kraaimaat FW, Geenen R, Bijlsma JWJ. Physical disability and psychological well being in recent onset rheumatoid arthritis. J Rheumatol 1994;21:28-32.

van der Heide A, Jacobs JWG, Biljsma JWJ, Heurkens AM, van Booma-Frankfort C, van der Veen MJ, Hofman DM, van Albada-Kuipers GA, ter Borg EJ, Brus HL, Dinant HJ, Kruize AA, Schenk Y. The effectiveness of early treatment with 'second-line' anti-rheumatic drugs. A randomized controlled trial. Ann Intern Med 1996;124:699-707.

van der Heijde DMFM, van Leeuwen MA, van Riel PLCM, Koster AM, van't Hof MA, van Rijswijk MH, van de Putte LBA. Biannual radiographic assessment of hands and feet in a three-year prospective follow-up of patients with early rheumatoid arthritis. Arthritis Rheum 1992;35:26-34.

van der Heijde DMFM, van't Hof MA, van Riel PLCM, van de Putte LBA. Development of a disease activity score based on judgement in clinical practice by rheumatologists. J Rheumatol 1993;20:579-581.

van der Heijde DMFM. Impact of imaging in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003;17:783-790.

Hollander M, Wolfe DA. Non-parametric statistical methods (2nd edition). New York: Wiley, 1999.

Holsti Ö, Rantasalo V. On the occurrence of arthritis in Finland. Acta Med Scand 1936;88:180-195.

Holte HH, Tambs K, Bjerkedal T. Becoming a disability pensioner with rheumatoid arthritis in Norway 1971-1990. J Rheumatol 2001;28:54-61.

Homik JE, Suarez-Almazor M. An economic approach to health care. Best Pract Res Clin Rheumatol 2004;18:203-218.

Häkkinen A, Sokka T, Lietsalmi A, Kautiainen H, Hannonen P. Effects of dynamic strength training on physical function, Valpar 9 work sample test, and working capacity in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2003;49:71-77.

Häkkinen A, Sokka T, Hannonen P. A home-based two-year strength training period in early rheumatoid arthritis led to good long-term compliance: a five-year followup. Arthritis Rheum 2004;51:56-62.

International Classification of Functioning, Disability and Health. Geneva: World Health Organization; 2001.

van Jaarsveld C, Jacobs J, Schrijvers A, van Albada-Kuipers G, Hofman D, Bijlsma J. Effects of rheumatoid arthritis on employment and social participation during the first years of disease in The Netherlands. Br J Rheumatol 1998;37:848-53.

Johannesson M. The willingness to pay for health changes, the human capital approach and the external costs. Health Policy 1996;36:231-244.

Jonsson B, Rehnberg C, Borgquist L, Larsson SE. Locomotion status and costs in destructive rheumatoid arthritis. A comprehensive study of 82 patients from a population of 13,000. Acta Orthop Scand. 1992;63:207-12.

Jonsson D, Husberg M. Socioeconomic costs of rheumatic diseases. Implications for technology assessment. Int J Technol Assess Health Care. 2000;16:1193-2000.

Jäntti J, Aho K, Kaarela K, Kautiainen H. Work disability in an inception cohort of patients with seropositive rheumatoid arthritis: a 20 year study. Rheumatology 1999;38:1138-41.

Kaarela K, Lehtinen K, Luukkainen R. Work capacity of patients with inflammatory joint diseases: an eight-year follow-up study. Scand J Rheumatol 1987;16:403-406.

Kaipiainen-Seppänen O, Aho K, Isomäki H, Laakso M. Shift in the incidence of rheumatoid arthritis toward elderly patients in Finland during 1975-1990. Clin Exp Rheumatol 1996;14:537-542.

Kaipiainen-Seppänen O, Aho K. Incidence of chronic inflammatory joint diseases in Finland in 1995. J Rheumatol 2000;27:94-100.

Kaipiainen-Seppänen O. Nivelreuman epidemiologia. Duodecim 2004;120:283-287.

Katz PP. The impact of rheumatoid arthritis on life activities. Arthritis Care Res 1995;8:272-278.

KELA – the Social Insurance Institution of Finland. A guide to benefits. Vantaa: Edita Oy; 2000.

Kessler RC, Barber C, Beck A, Berglund P, Cleary PD, McKenas D, Pronk N, Simon G, Stang P, Ustun TB, Wang P. The World Health Organization Health and Work Performance Questionnaire (HPQ). J Occup Environ Med 2003;45:156-174.

Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J Med 1995;333:142-146.

Kirwan JR. Links between radiological change, disability, and pathology in rheumatoid arthritis. J Rheumatol 2001;28:881-886.

Klareskog L, Alfredsson L, Rantapaa-Dahlqvist S, Berglin E, Stolt P, Padyukov L. What precedes development of rheumatoid arthritis? Ann Rheum Dis. 2004 Nov;63 Suppl 2:ii28-ii31.

Klareskog L, van der Heijde DM, de Jager JP, Gough A, Kalden J, Malaise M, Martin Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each

treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-681.

Kobelt G, Eberhardt K, Jonsson L, Jonsson B. Economic consequences of the progression of rheumatoid arthritis in Sweden. Arthritis Rheum. 1999;42:347-56.

Koopmanschap MA, Rutten FF. A practical guide for calculating indirect costs of disease. Pharmacoeconomics. 1996;10:460-466.

Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, Paimela L, Blåfield H, Puolakka K, Möttönen T; FIN-RACo Trial Group. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: Five-year experience from the FIN-RACo study. Arthritis Rheum. 2004;50:2072-2081.

Korthals-de Bos I, Van Tulder M, Boers M, Verhoeven AC, Ader HJ, Bibo J, Boonen A, van der Linden S. Indirect and total costs of early rheumatoid arthritis: a randomized comparison of combined step-down prednisolone, methotrexate, and sulfasalazine with sulfasalazine alone. J Rheumatol 2004;31:1709-1716.

Kuiper S, van Gestel AM, Swinkels HL, de Boo TM, da Silva JA, van Riel PLCM. Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis. J Rheumatol 2001;28:1809-16.

Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics 2004;22(Suppl 2):1-12.

Lacaille D, Sheps S, Spinelli JJ, Chalmers A, Esdaile JM. Indentification of modifiable work-related factors that influence the risk of work disability in rheumatoid arthritis. Arthritis Rheum 2004;51:843-852.

Lacaille D. Arthritis and employment research: where are we? Where do we need to go? J Rheumatol 2005;72:Suppl.42-45.

Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, van Denderen JC, Westedt ML, Peeters AJ, Dijkmans BA, Jacobs P, Boonen A, van der Heijde DM, van der Linden S. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-356.

Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, Hazes JMW. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446-451.

Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn 1977;18:481-491.

Larsen A, Thoen J: Hand radiography of 200 patients with rheumatoid arthritis repeated after an interval of one year. Scand J Rheumatol 1987;16:395-401.

Lee SJ-A, Kavanaugh A. Pharmacological treatment of established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003;17:811-829.

Leigh JP, Fries JF. Predictors of disability in a longitudinal sample of patients with rheumatoid arthritis. Ann Rheum Dis 1992;51:581-587.

Liljas B. How to calculate indirect costs in economic evaluations. Pharmacoeconomics. 1998; 13:563-569.

Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedvedt FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR, Maini RN. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594-1602.

Lofland JH, Locklear JC, Frick KD. Different approaches to valuing the lost productivity of patients with mignaine. Pharmacoeconomics 2001;19:917-925.

Lofland JH, Pizzi L, Frick KD. A review of health-related workplace productivity loss instruments. Pharmacoeconomics 2004;22:165-184.

Lubeck DP. The costs of musculoskeletal disease: health needs assessment and health economics. Best Pract Res Clin Rheumatol 2003;17:529-539.

Luukkainen R, Kajander A, Isomäki H. Effect of gold on progression of erosions in rheumatoid arthritis: better results with early treatment. Scand J Rheumatol 1977;6:189-192.

MacGregor AJ, Silman AJ. Classification and epidemiology. In: Hochberg MC et al., ed. Rheumatology. St Louis: Mosby; 2003: 757-763.

Maillefert JF, Combe B, Goupille P, Cantagrel A, Dougados M. Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. Ann Rheum Dis 2003;62:764-766.

Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, Antoni C, Leeb B, Elliott MJ, Woody JN, Schaible TF, Feldmann M. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552-1563.

March L, Lapsley H. What are the costs to society and the potential benefits from the effective management of early rheumatoid arthritis? Best Pract Res Clin Rheumatol 2001;15:171-185.

Marnetoft SU, Selander J. Long-term effects of early versus delayed vocational rehabilitation – a four-year follow-up. Disabil Rehabil 2002;24:741-5.

Matteson EL. Extra-articular features of rheumatoid arthritis and systemic involvement. In: Hochberg MC et al., ed. Rheumatology. St Louis: Mosby; 2003:781-792.

Mau W, Bornmann M, Weber H, Weidemann H, Hecker H, Raspe H. Prediction of permanent work disability in a follow-up study of early rheumatoid arthritis: results of a tree structured analysis using RECPAM. Br J Rheumatol 1996;35:652-9.

Mau W, Bornmann M, Weber H. Arbeitsfähigkeit im ersten Jahr der chronischen Polyarthritis. Ein Vergleich mit Pflichtmitgliedern der gesetzlichen Krankenversicherung. Z Rheumatol 1997;56:1-7.

McFarlane AC, Brooks PM. The assessment of disability and handicap in musculoskeletal disease. J Rheumatol 1997;24:985-989.

Meenan RF, Yelin EH, Nevitt M, Epstein WV. The impact of chronic disease: a sociomedical profile of rheumatoid arthritis. Arthritis Rheum 1981;24:544-549.

Merkesdal S, Ruof J, Schoffski O, Bernitt K, Zeidler H, Mau W. Indirect medical costs in early rheumatoid arthritis: Composition of and changes in indirect costs within the first three years of disease. Arthritis Rheum 2001;44:528-534.

Merkesdal S, Ruof J, Huelsemann JL, Mittendorf T, Handelmann S, Mau W, Zeidler H. Indirect cost assessment in patients with rheumatoid arthritis (RA): comparison of data from the health economic patient questionnaire HEQ-RA and insurance claims data. Arthritis Rheum 2005;53:234-40.

Mitchell JM, Burkhauser RV, Pincus T. The importance of age, education, and comorbidity in the substantial earmings losses of individuals with symmetric polyarthritis. Arthritis Rheum 1988;31:348-357.

Munro R, Hampson R, McEntegart A, Thomson A, Madhok R, Capell H. Improved functional outcome in patients with early rheumatoid arthritis treated with intramuscular gold: results of a five year prospective study. Ann Rheum Dis 1998;57:88-93.

Mutru O, Laakso M, Isomäki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. Br J Med 1985;290:1811-1813.

Myllykangas-Luosujärvi R, Aho K, Kautiainen H, Isomäki H. Shortening of life span and causes of excess mortality in a population-based series of subjects with rheumatoid arthritis. Clin Exp Rheumatol 1995;13:149-153.

Mäkisara GL, Mäkisara P. Prognosis of functional capacity and work capacity in rheumatoid arthritis. Clin Rheumatol 1982;1:117-125.

Möttönen T, Paimela L, Ahonen J, Helve T, Hannonen P, Leirisalo-Repo M. Outcome in patients with early rheumatoid arthritis treated according to the “sawtooth” strategy. Arthritis Rheum 1996;39:996-1005.

Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blåfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimäki I, Forsberg S, Koota K, Friman C; FIN-RACo Trial Group. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomised trial. Lancet 1999;353:1568-1573.

Möttönen T, Hannonen P, Korpela M, Nissilä M, Kautiainen H, Ilonen J, Laasonen L, Kaipiainen-Seppänen O, Franzen P, Helve T, Koski J, Gripenberg-Gahmberg M, Myllykangas-Luosujärvi R, Leirisalo-Repo M; FIN-RACo Trial Group. Delay to institution of therapy and induction of remission using single-drug or combination–disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 2002;46:894-898.

Newhall-Perry K, Law NJ, Ramos B, Sterz M, Wong WK, Bulpitt KJ, Park G, Lee M, Clements P, Paulus HE. Direct and indirect costs associated with the onset of seropositive rheumatoid arthritis. Western consortium of practicing rheumatologists. J Rheumatol. 2000;27:1156-1163.

Newman S, Mulligan K. The psychology of rheumatic diseases. Best Pract Res Clin Rheumatol 2000;14:773-786.

Nicolau G, Yogui MM, Vallochi TL, Gianini RJ, Laurindo IM, Novaes GS. Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. J Rheumatol 2004;31:1293-1296.

O’Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Echhoff PJ, Garwood V, Maloley P, Klassen LW, Wees S, Klein H, Moore GF. Treatment of rheumatoid arthritis with

methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334:1287-1291.

O'Dell JR. Treating rheumatoid arthritis early: a window of opportunity. Arthritis Rheum 2002;46:283-285.

O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Echhoff PJ, Fernandez A, Blakely K, Wees S, Stoner J, Hadley S, Felt J, Palmer W, Waytz P, Churchill M, Klassen L, Moore G. Treatment of rheumatoid arthrtitis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controled trial. Arthritis Rheum 2002;46:1164-1170.

O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004;350:2591-2602.

O'Dell JR. Rheumatoid arthritis initial therapy: unanswered questions. J Rheumatol 2005;72 Suppl.14-16.

Ollier WER, Harrison B, Symmons D. What is the natural history of rheumatoid arthritis? Best Pract Res Clin Rheumatol 2001;15:27-48.

Ory PA. Radiography in the assessment of musculoskeletal conditions. Best Pract Res Clin Rheumatol. 2003;17:495-512.

van Paassen P, Damoiseaux J, Cohen Trervaert JW. Laboratory assessement in musculoskeletal conditions. Best Pract Res Clin Rheumatol 2003:17:475-494.

Paulus HE, Egger MJ, Ward JR, Williams HJ. Analysis of improvement of individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on the findings in patients treated with placebo. Arthritis Rheum 1990;33:477-484.

Pham B, Cranney A, Boers M, Verhoeven AC, Wells G, Tugwell P. Validity of area-under-the-curve analysis to summarize effect in rheumatoid arthritis clinical trials. J Rheumatol 1999;26:712-716.

Pinals R, Masi A, Larsen R, and the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308-15.

Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum 1984;27:864-872.

Pincus T, Marcum SB, Callahan LF. Long.-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second-line drugs and prednisone. J Rheumatol 1992;19:1885-1894.

Pincus T, Sokka T. How can the risk of long-term consequences of rheumatoid arthritis be reduced. Best Pract Res Clin Rheumatol 2001;15:139-170.

Pincus T, Ferraccoli G, Sokka T, Larsen A, Rau R, Kushner I, Wolfe F. Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. Rheumatology (Oxford) 2002;41:1346-1356.

Pincus T, Sokka T. Quantitative measures for assessing rheumatoid arthritis in clinical trials and clinical care. Best Pract Res Clin Rheumatol. 2003;17:753-781.

Pincus T, Strand V, Koch G, Amara I, Crawford B, Wolfe F, Cohen S, Felson D. An index of the three core data set patient questionnaire measures distinguishes efficacy of active treatment from that of placebo as effectively as the American College of Rheumatology 20% response criteria (ACR20) or the Disease Activity Score (DAS) in a rheumatoid arthritis clinical trial. Arthritis Rheum 2003; 48:625-630.

Pincus T, Sokka T, Kavanaugh A. Relative versus absolute goals of therapies for RA: ACR20 or ACR50 responses versus target values for “near remission” of DAS or single measures. Clin Exp Rheumatol 2004:22:S50-S56.

Plant MJ, Williams AL, O'Sullivan MM, Lewis PA, Coles EC, Jessop JD. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. Arthritis Rheum 2000;43:1473-1477.

Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Arthritis Rheum 1995;38:44-48.

Prevoo ML, van Gestel AM, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. ARA preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35:1101-1105.

Pugner KM, Scott DI, Holmes JW, Hieke K. The costs of rheumatoid arthritis: An international long-term view. Semin Arthritis Rheum. 2000;29:305-320.

Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Grenstein A, Brown A, Brown C, Fraser A, Jarret S, Emery P. Very early treatment with infliximab in addition to methotreaxate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month ranomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:27-35.

Reisine ST, Grady KE, Goodenow C, Fifield J. Work disability among women with rheumatoid arthritis: the relative importance of disease, social, work, and family factors. Arthritis Rheum 1989;32:538-543.

Reisine S, McQuillan J, Fifield J. Predictors of work disability in rheumatoid arthritis patients. A five-year followup. Arthritis Rheum 1995;38:1630-7.

van Riel PLCM, Haagsma CJ, Furst DE. Pharmacotherapeutic combination strategies with disease-modifying antirheumatic drugs in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 1999;13:689-700.

van Riel PLCM, van Gestel AM, Scott DL. EULAR handbook of clinical assessments in rheumatoid arthritis. Nijmegen: Van Zuiden Communications B.V.; 2000.

van Riel PLCM, van Gestel AM, Welsing PMJ. Evaluation and outcome of the patient with established rheumatoid arthritis. In: Hochberg MC et al., ed. Rheumatology. St Louis: Mosby; 2003:893-905.

de Roos, AJ, Callahan LF. Differences by sex in correlates of work status in rheumatoid arthritis patients. Arthritis Care Res 1999;12:381-291.

Ruof J, Hulsemann JL, Mittendorf T, Handelmann S, von der Schulenburg JM, Zeidler H, Merkesdal S. Costs of rheumatoid arthritis in Germany: a micro-costing approach based on healthcare payer's data sources. Ann Rheum Dis 2003;62:544-549.

Scharloo M, Kaptein AA, Weinman JA, Hazes JMW, Breedveld FC, Rooijmans HGM. Predicting functional status in patients with rheumatoid arthritis. J Rheumatol 1999;26:1686-1693.

Scott DL, Pugner K, Kaarela K, Doyle DV, Woolf A, Holmes J, Hieke K. The links between joint damage and disability in rheumatoid arthritis. Rheumatology (Oxford) 2000;39:122-132.

Scott DL, Garrood T. Quality of life measures: use and abuse. Best Pract Res Clin Rheumatol 2000;14:663-687.

Scott DL, Smith C, Kingsley G. What are the consequences of early rheumatoid arthritis for the individual? Best Pract Res Clin Rheumatol 2005:19:117-136.

Shanahan EM, Smith MD. Rheumatoid arthritis, disability and workplace. Best Pract Res Clin Rheumatol 1999;13:675-688.

Sharp JT, Lidsky MD, Collins LC, Moreland J. Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Arthritis Rheum 1971;14:206-220.

Silman AJ, Hochberg MC. Epidemiology of the rheumatic diseases. 2nd edn. Oxford: Oxford University Press; 2001.

Smedstad LM, Kvien TK, Moum T, Valgum P. Life events, psychosocial factors, and demographic variables in early rheumatoid arthritis: relations to one-year changes in functional disability. J Rheumatol 1995;22:2218-2225.

Smedstad LM, Kvien TK, Moum T, Valgum P. Correlates of patients' global assessment of arthritis impact. A 2-year study of 216 patients with rheumatoid arthritis. Scand J Rheumatol 1997;26:259-265.

Sokka T, Kautiainen H, Möttönen T, Hannonen P. Work disability in rheumatoid arthritis 10 years after the diagnosis. J Rheumatol 1999;26:1681-5.

Sokka T, Kankainen A, Hannonen P. Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. Arthritis Rheum 2000;43:386-9.

Sokka T, Pincus T. Markers for work disability in rheumatoid arthritis. J Rheumatol 2001;28:1718-22.

Sokka T. Assessment of pain in patients with rheumatic diseases. Best Pract Res Clin Rheumatol 2003;17:427-449 (a).

Sokka T. Work disability in early rheumatoid arthritis. Clin Exp Rheumatol. 2003;21:S71-74 (b).

Sokka T, Kautiainen H, Häkkinen A, Hannonen P. Radiographic progression is getting milder in patients with early rheumatoid arthritis. Results of 3 cohorts over 5 years. J Rheumatol 2004;31:1073-1082.

St Clair EW, van der Heijde DM, Smolen JS, Maini RW, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D. Activity-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432-3443.

Stenger AAM, van Leeuwen MA, Houtman PM, Bruyn GAW, Speerstra F, Barendsen BC, Velthuysen E, van Rijswijk MH. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Br J Rheumatol 1998;37:1157- 1163.

Stewart WF, Ricci JA, Chee E, Morganstein D. Lost productive work time costs from health conditions in the United States: results from the American productivity audit. J Occup Environ Med 2003;45:1234-1246 (a).

Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. JAMA. 2003;290:2443-2454 (b).

Straaton KV, Harvey M, Maisiak R. Factors associated with successful vocational rehabilitation in person with arthritis. Arthritis Rheum 1992:35:503-510.

Straaton KV, Maisiak R, Wrigley J, White M, Johnson P, Fine P. Barriers to return to work among persons unemployed due to arthritis and musculoskeletal disorders. Arthritis Rheum 1996;39:101-9.

Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, Fox R, Moreland L, Olsen N, Furst D, Caldwell J, Kaine J, Sharp J, Hurley F, Loew-Friedrich I. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med. 1999;159:2542-50.

Stucki G, Kroeling P. Physical therapy and rehabilitation on the management of rheumatic disoreders. Best Pract Res Clin Rheumatol 2000;14:751-771.

Stucki G, Sigl T. Assessment of the impact of disease on the individual. Best Pract Res Clin Rheumatol 2003;17:451-473.

Stucki G, Cieza A. The international classification of functioning, disability and health (ICF) core sets for rheumatoid arthritis: A way to specify functioning. Ann Rheum Dis. 2004;63:40-45.

Söderlin MK, Kautiainen H, Jonsson D, Skogh T, Leirisalo-Repo M. The costs of early inflammatory joint disease: a population-based study in southern Sweden. Scand J Rheumatol. 2003;32:216-24.

Tengstrand B, Ahlmen M, Hafström I. The influence of sex on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. J Rheumatol 2004;31:214-222.

Townsend HB, Saag KG. Glucocorticoid use in rheumatoid arthritis: Benefits, mechanisms, and risks. Clin Exp Rheumatol 2004;22:S77-S82.

Tsakonas E, Fitzgerald A, Fitzcharles M , Cividino A, Thorne J, M´Seffer A, Joseph L, Bombardier C, Esdaile JM. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J Rheumatol 2000;27:623-9.

Tugwell P, Boers M. OMERACT Committee. Proceedings of the OMERACT Conferences on Outcome Measures in Rheumatoid Arthritis Clinical Trials, Maastrict, Netherlands. J Rheumatol 1993;20:527-591.

Verstappen SM, Bijlsma JW, Verkleij H, Buskens E, Blaauw AA, ter Borg EJ, Jacobs JW; Utrecht Rheumatoid Cohort Study Group. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. Arthritis Rheum. 2004;51:488-497.

Verstappen SM, Boonen A, Bijlsma JW, Verkleij H, Schenk Y, van Albada-Kuipers GA, Hofma DM, Jacobson JW. Working status among Dutch patients with rheumatoid arthritis: work disability and working conditions. Rheumatology (Oxford) 2005;44:202-206 (a).

Verstappen SM, Boonen A, Verkleij H, Bijlsma JW, Buskens E, Jacobs JW. Productivity costs among patients with rheumatoid arthritis: the influence of methods and sources to value loss of productivity. Ann Rheum Dis. 2005 May 18; [Epub ahead of print] (b).

Vliet Vlieland TPM. Rehabilitation of people with rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003;17:847-861

Walji S, Bykerk VP. Rheumatoid arthritis: is the disease becoming milder or is treatment improving? J Rheumatol 2004;31:1023-1025.

Wang PS, Beck A, Berglund P, Leutzinger JA, Pronk N, Richling D, Schenk TW, Simon G, Stang P, Ustun TB, Kessler RC. Chronic medical conditions and work performance in the health and work performance questionnaire calibration surveys. J Occup Environ Med. 2003;45:1303-1311.

Wegman DH. Older workers. Occup Med 1999;14:537-57.

Welsing PMJ, van Gestel AM, Swinkels HL, Kiemeney LAML, van Riel PLCM. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44:2009-2017.

Welsing PMJ, Landewe RB, van Riel PLCM, Boers M, van Gestel AM, van der Linden S, Swinkels HL, van der Heijde DMFM. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082-2093.

Wiles NJ, Dunn G, Barrett EM, Harrison BJ, Silman AJ, Symmons DPM. One year followup variables predict disability 5 years after presentation with inflammatory polyarthritis with greater accuracy than at baseline. J Rheumatol 2000;27:2360-2366.

Wiles NJ, Dunn G, Barrett EM, Harrison BJ, Silman AJ, Symmons DPM. Associations between demographic and disease-related variables and disability over the first five years of inflammatory polyarthritis: a longitudinal analysis using generalized estimating equations. J Clin Epidemiol 2000;53:988-996.

Wolfe F, Cathey M. The assessment and prediction of functional disability in rheumatoid arthritis. J Rheumatol 1991;18:1298-306.

Wolfe F, Hawley D. The longterm outcomes of rheumatoid arthritis: Work disability: a prospective 18 year study of 823 patients. J Rheumatol 1998;25:2108-17.

Wolfe F. A reappraisal of HAQ disability in rheumatoid arthritis. Arthritis Rheum 2000:43:2751-2761.

Wolfe F. Which HAQ is best? A comparison of the HAQ, MHAQ and RA-HAQ, a difficult 8 item HAQ (DHAQ), and a recorded 20 item HAQ (HAQ20): analysis in 2491 rheumatoid arthritis patients following leflunomide initiation. J Rheumatol 2001;28:982-989.

Woolf AD. History and physical examination. Best Pract Res Clin Rheumatol 2003;17:381-402.

Yelin E, Meenan R, Nevitt M, Epstein W. Work disability in rheumatoid arthritis: effects of disease, social, and work factors. Ann Intern Med 1980;93:551-556.

Yelin E, Hanke C, Epstein W. The work dynamics of the person with rheumatoid arthritis. Arthritis Rheum 1987;30:507-512.

Yelin E. Arthritis: the cumulative impact of a common chronic condition. Arthritis Rheum 1992;35:489-497.

Yelin E, Callahan LF. The economic cost and social and psychological impact of musculoskeletal conditions. Arthritis Rheum 1995;38:1351-1362.

Yelin E, Trupin L, Katz P, Lubeck D, Rush S, Wanke L. Association between etanercept use and employment outcomes among patients with rheumatoid arthritis. Arthritis Rheum 2003;48:3046-54.

Young A, Dixey J, Kulinskaya E, Cox N, Davies P, Devlin J, Emery P, Gough A, James D, Prouse P, Williams P, Winfield J. Which patients stop working because of rheumatoid arthritis? Results of five years´ follow up in 732 patients from the Early RA Study (ERAS). Ann Rheum Dis 2002;61:335-40.

13 APPENDICES

Appendix 1

CALCULATION OF SICKNESS ALLOWANCE (sums in euros)

Amount of sickness allowance is calculated according to the preceding year's personal income, as stated in Finnish law. Income = annual income assessed by tax authorities at the last taxation, with income acquisition expenses, expenses for travel to and from work, and trade union dues deducted. All monetary values are in euros.

1993

The minimum allowance, payable to all residents of Finland, is 10.63 per day.

If income is less than	6,379.37
the allowance is	10.63 + 30% of (income/300weekdays).
If income is	6,379.37 to 19,222.20
the allowance is	17.00 + 66% of (income minus 6,379.37)/300.
If income is	19,222.20 to 32,036.44
the allowance is	45.25 + 40% of (income minus 19,222.20)/300.
If income is more than	32,036.44
the allowance is	62.34 + 25% of (income minus 32,036.44)/300.

1994

The minimum allowance, payable to all residents of Finland, is 10.92 per day.

If income is less than	6,379.37
the allowance is	10.63 + 30% of (income/300).

If income is less than 6,042.99, then the allowance is increased by 2.8%.

If income is 6,379.37 to 19,222.20
the allowance is 17.29 + 66% of (income minus 6,379.37)/300.

If income is 19,222.20 to 32,036.44
the allowance is 45.54 + 40% of (income minus 19,222.20)/300.

If income is more than 32,036.44
the allowance is 62.63 + 25% of (income minus 32,036.44)/300.

1995

The minimum allowance, payable to all residents of Finland, is 11.08 per day.

If income is less than 6,470.19
the allowance is 10.63 + 30% of (income/300).

If income is 6,470.19 to 19,222.20
the allowance is 17.39 + 66% of (income minus 6,470.19)/300.

If income is 19,496.34 to 32,492.23
the allowance is 46.04 + 40% of (income minus 19,496.34)/300.

If income is more than 32,492.23
the allowance is 63.36 + 25% of (income minus 32,492.23)/300.

1996

If income is less than 880.57
no allowance is paid, but based on a means test, allowance of 10.09 is possible.

If income is	880.57 to 22,894.69
the allowance is	70% of (0.955 x income minus 840.94)/300.

If income is	22,894.69 to 35,222.61
the allowance is	49.05 + 40% of (0.955 x income minus 21,864.43)/300.

If income is more than	35,222.61
the allowance is	64.75 + 25% of (0.955 x income minus 33,637.59)/300.

1997

If income is less than	894.65

no allowance is paid, but based on a means test, allowance of 10.09 is possible.

If income is	894.65 to 23,296.23
the allowance is	70% of (0.955 x income minus 854.39)/300.

If income is	23,296.23 to 35,842.52
the allowance is	49.92 + 40% of (0.955 x income minus 22,247.90)/300.

If income is more than	35,842.52
the allowance is	65.90 + 25% of (0.955 x income minus 34,229.61)/300.

Appendix 2

CALCULATION OF THE MONETARY VALUE OF EACH PATIENT'S PRODUCTIVITY

I Patients with data on sickness absence and sickness allowance

Calculation of the **annual income** assessed by tax authorities before the patients contracted RA was performed by doing the calculation formula of allowances backwards.

When, the first sickness allowance was paid in 1993

If allowance was 10.63 (minimum) to 17.00,
income was 1000 x (daily allowance minus 10.63).
If allowance was 17.00 to 45.24,
income was 454.55 x daily allowance minus 1,350.00
If allowance was 45.25 to 62.33,
income was 750 x daily allowance minus 14,715.00.
If allowance was 62.34 or over,
income was 1200 x daily allowance minus 42,768.00.

Incomes are adjusted for a child supplement to the sickness allowance (1.45 for 1 child, 2.90 for ≥2).

When, the first sickness allowance was paid in 1994

If allowance was 10.92 (minimum) to 17.28,
income was 1000 x (daily allowance minus 10.92).
If allowance was 17.29 to 45.53,
income was 454,55 x daily allowance minus 1,350.00.
If allowance was 45.54 to 62.62,
income was 750 x daily allowance minus 14,715.00.

If allowance was 62.64 or more,
income was 1200 x daily allowance minus 42,768.00.

When, the first sickness allowance was paid in 1995

If allowance was 11.08 to 17.38,
income was 1000 x (daily allowance minus 11.08).
If allowance was 17.39 to 46.03,
income was 454.55 x daily allowance minus 1,434.00.
If allowance was 46.04 to 63.35,
income was 750 x daily allowance minus 15,033.00.
If allowance was 63.36 or more,
income was 1200 x daily allowance minus 43,538.00.

When, the first sickness allowance was paid in 1996

If allowance was less than 49.06,
income was 448.766 x daily allowance + 880.57.
If allowance was 49.06 to 64.75
income was 785.34 x daily allowance + 22,894.69.

When, the first sickness allowance was paid in 1997

If allowance was less than 49.93,
income was 488.766 x daily allowance + 894.65.

The last RA patients in the study received their first sickness allowances in 1996 (for 4 patients) and in 1997 (for 1 patient).

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According to income tax law (TVL §93–95), the deducted average **income acquisition expenses** in each year (from the National Board of Taxation) were added, except for self-employed persons. FIM = Finnish marks; € = euros.

Year	Number of people	Income acquisition expenses, FIM	Journey expenses, FIM	Trade dues, FIM	Altogether, FIM	Expenses per person, €
1992	2,450,000	3,945,000	3,105,000	2,055,000	9,105,000	625.04
1993	2,472,075	3,646,000	3,083,000	2,413,000	9,142,000	621.98
1994	2,447,112	3,591,000	3,262,000	2,648,000	9,501,000	653.00
1995	2,462,947	2,788,000	3,066,000	2,633,000	8,487,000	579.55
1996	2,488,687	2,854,000	3,237,000	2,688,000	8,779,000	593.29
1997	2,507,555	3,427,000	3,370,000	2,618,000	9,415,000	631.49
1998	2,543,626	3,535,000	3,410,000	2,643,000	9,588,000	633.97
1999	2,582,452	4,121,000	3,848,000	2,634,000	10,603,000	690,54
2000	2,625,553	4,735,000	4,378,000	2,687,000	11,800,000	755.89

Income after the first year was calculated by use of annual income indices of various branches of the economy (process industry, private service, building, transport, municipalities, state, self-employed farmers, other self-employed persons) from Statistics Finland (www.stat.fi).

For wage and salary earners, average supplementary **social welfare expenses** (sickness insurance, pension insurance, unemployment insurance, accident insurance, group life insurance) were added to income in each year:

1993	38.0%
1994	37.0%
1995	35.0%
from 1996 onwards	32.2%

For self-employed farmers, the corresponding social insurance percentages were:

1993	11.68%
1994	12.23%
1995	11.50%
1996	12.84%
1997	13.02%
1998	12.85%
1999	12.95%
2000	12.88%

For other self-employed persons, the statutory social insurance percentages were:

1993	22.00%
1994	22.55%
1995	22.25%
1996	21.60%
1997	21.90%
1998	21.90%
1999	21.80%
2000	21.80%

***

II Patients with data on sickness absence but without data on allowances paid

Wage and salary earners

The average income from each job in 2002 came from Statistics Finland. Income in the preceding years was calculated by indices of wages and salaries (general index and separately the index of transport jobs and of building jobs). Average supplementary social welfare expenses were added to income.

Self-employed persons

Average income declared to the Farmer's Pension Insurance Institution and the Entrepreneur's Pension Insurance Institution in each year was obtained. Studies indicate that declarations of income made to pension insurance institutions are deliberately about 20% low. Consequently, 20% was added to the income as was the statutory social insurance percentages.

Appendix 3

CALCULATION OF THE MONETARY VALUE OF EACH PATIENT'S LOST PRODUCTIVITY

The value of each patient's annual productivity was adjusted to 2002 prices by the general index of wages and salaries. Annual productivity was divided by 365 to yield productivity per day. Productivity per calender day was used, because number of working days per year differs between individuals. Mean daily productivity from 1993 over 2000 was calculated.

The value of lost productivity was calculated by multiplying each patient's daily productivity by the number of days of sickness absence periods.