The impact of rheumatoid arthritis and treatment on patients' lives

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, debilitating disease that significantly impacts patients' quality of life and socioeconomic productivity. On a personal level, RA has a significant socioeconomic impact on patients' lives, being ranked among the highest of all chronic diseases for its effect on health-related quality of life (HRQoL), and limitations in physical function as well as increased pain and fatigue affect patients' attendance at paid work, their work performance within and outside the home, and their participation in family, social, and leisure activities. Additional paid or unpaid support, as well as increased flexibility and job modifications from employers, are often required so that patients can meet their role obligations. Disease-related reductions in work and household productivity are not just due to the physical limitations posed by RA; mental/emotional limitations also play a key role in reducing patients' HRQoL and productivity. Newer, effective treatments, such as tumour necrosis factor (TNF) inhibitors, improve the signs and symptoms of disease, inhibit progression of joint damage, and improve physical function and HRQoL. A recently available TNF inhibitor for RA, certolizumab pegol, has been shown to increase productivity outside and within the home and participation in family, social, and leisure activities as well as rapidly improve physical function, fatigue, and pain. Due to the importance of these parameters to patients, new therapies are increasingly assessed based on their ability to improve HRQoL, productivity, and participation. These extend the more traditional measures of efficacy into outcomes that are more central to patients' daily lives.

What is health-related quality of life?

An individual's overall quality of life is composed of a wide range of factors, including physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment (1, 2). Health-related quality of life (HRQoL) is that part of a patient's perception of their position in life, in the context of their local culture and value systems, and in relation to their goals, expectations, standards, and concerns that are affected by their health status (3, 4). Thus, a patient's HRQoL is the extent to which their usual or expected physical, emotional, and social well-being are impacted by their medical condition and/or its treatment.

Impact of rheumatoid arthritis on HRQoL

Patients with rheumatoid arthritis (RA) have significantly impaired HRQoL, especially in terms of physical functioning, pain, and vitality, but also in terms of their emotional state (5, 6), and patients report that these facets of the disease are more important than traditional clinical measures from their perspective (7). The disease-related reductions in the physical and mental/emotional aspects of HRQoL are influenced by each other.

Relief of pain is one of the most important treatment outcomes for patients with RA, and one of the main reasons they seek medical care (8, 9). Patients with RA describe associated fatigue as overwhelming and more intense than typical tiredness experienced before being diagnosed with RA (8, 10). Pain and fatigue are both associated with impairments in physical function (11-13) and significantly impact patients' HRQoL by restricting their usual activities, including social and work functions. As such, RA has a significant impact on patients' financial and social well-being (14). Depressed mood, as assessed by various measures including Geriatric Depression Scale (GDS), Hospital Anxiety and Depression (HAD) Scale (HADS), Pain Distress Inventory (PDI),

Inventory to Diagnose Depression (IDD), Profile of Mood States (POMS), Center for Epidemiological Studies Depression Scale (CES-D), Arthritis Impact Measurement Scales (AIMS) depression scores, and the depression subscale of the Psychological Symptom Checklist has been found to range between 13% and 20% in patients with RA (15), which is significantly more common than in the general healthy population.

Comparative data from clinical trials in RA show some differences in the effects of RA on physical function and HRQoL between patients with early and late disease. An analysis of disability (as measured by the Health Assessment Questionnaire Disability Index [HAQ-DI]) versus disease duration by Pollard *et al*. found that patients with early disease had greater impairments in physical function (16). Furthermore, comparison of HRQoL (as measured by the Short-Form 36 [SF-36] health survey) in patients with RA found that HRQoL was more negatively impacted in early RA than in late disease (17).

Impact of treatment on HRQoL

Treatment-related reductions in disability, pain, and fatigue, reflected in improvements in HRQoL, allow patients to continue to work inside and outside the home, thereby decreasing the socioeconomic burden of disease. In addition, reductions in disability, pain, and fatigue, and resultant improvements in work/home productivity, also improve patient's mental well-being. Due to the importance of these outcomes to patients, and the substantial economic and emotional costs of RA, new therapies are increasingly assessed according to their ability to improve productivity and HRQoL as well as traditional measures of efficacy. Furthermore, US Food and Drug Administration (FDA) guidance requests demonstration of improvement in physical function and HRQoL over the long-term (*e.g*. 24 months) for specific labeling related to these attributes.

Impact of disease modifying anti-rheumatic agents

Nonbiologic disease modifying antirheumatic agents (DMARDs) are used initially in the treatment of RA. Methotrexate (MTX), a synthetic DMARD, is the most commonly prescribed agent (either as monotherapy or in combination with other agents), and it improves disability to a greater extent than other DMARDs, such as hydroxychloroquine and injectable gold (18). In comparative studies, leflunomide has been shown to improve HRQoL to a greater extent than MTX, with advantages for leflunomide in the individual SF-36 domains of pain, vitality, and role emotional over 12 months and all eight domains over 24 months of treatment (19-21). In addition, fewer patients need to be treated with leflunomide than MTX to achieve clinically meaningful improvements in physical function and HRQoL. Apart from acquisition costs, treatment with either MTX or leflunomide has similar benefit/risk profiles and annual treatment-associated costs (22).

Impact of TNF inhibitors

The biologic agents, such as the tumour necrosis factor (TNF) inhibitors, represent more advanced therapies for RA. In addition to reducing signs and symptoms of disease and inhibiting progression of structural damage, they have led to low disease activity and remission of disease becoming goals of therapy that are not only achievable but maintained over several years of treatment. They also improve patient-reported HRQoL. The most recently available agent in this class, certolizumab pegol, has been shown to confer these benefits rapidly after treatment is started, which is also important from patients' perspective.

Clinical trials in early RA have shown that the TNF inhibitors etanercept, infliximab, and adalimumab in combination with MTX improve a variety of HRQoL measures compared with MTX alone (Table I) (23-29).

In a study comparing etanercept plus MTX with placebo plus MTX, more etanercept-treated patients achieved normal function after 52 weeks of treatment (based on a mean normal population-based HAQ-DI score of 0.49) (23, 29). Patients receiving infliximab plus MTX also reported statistically significant improvements in physical function after 1 year compared with those receiving placebo plus MTX (24), while in another study, initial treatment with infliximab plus MTX allowed more patients to achieve population norms for measures of pain and mental functioning over 2 years, and to approach those for physical functioning, than other treatment strategies including sequential monotherapy and step-up combination therapy (both starting with MTX) (25). After 2 years of treatment with adalimumab plus MTX, more patients reported clinically meaningful improvements in physical function (defined by ≥0.22 in HAQ-DI) than did those treated with either adalimumab monotherapy or MTX therapy (26), and patients treated with adalimumab plus MTX also approached US population norms for physical and mental health scores (27). Improvements in physical function over 56 weeks were also larger with adalimumab plus MTX than with MTX alone (28).

TNF inhibitors have also been shown to impact HRQoL in patients with longer-term disease and in studies in clinical practice rather than in randomised controlled trials (Table I) (30-37). Clinically meaningful improvements in HAQ-DI scores have been reported with etanercept (with or without MTX) from pooled studies of up to 4 years' duration with elderly patients (aged 65 years or older) (30). Improvements in physical function in this analysis were fastest in the first 3 months, and sustained for 6 months. In another study, patients with access to etanercept reported improved physical but not mental quality of life outcomes compared with patients who did not receive this treatment, due to lack of availability or insurance, over 1 year of study (although there were no restrictions on other RA treatments that the patients could have received) (31). One study with infliximab in long-term RA reported that most infliximab-treated patients achieved clinically meaningful improvements in disability after an average of 21 months' treatment in a real-life clinical setting (32). In two studies, patients receiving adalimumab plus MTX achieved clinically important and statistically significant improvements in health utility by week 12, which were sustained over 24 and

Table I. Improvements in physical function and HRQoL outcomes with TNF inhibitors in early and established RA.

Reference	Disease duration (mean)	Treatment arms (n) active and control	Outcome measures (mean) (time point)	Results active *vs*. control	*p*-value
Early RA					
Emery *et al*. 2008; Kekow *et al*. 2009 (COMET) (23, 29)	0.8 years	ETN + MTX (265) MTX (263)	HAQ-DI ≤0.5 HAQ-DI change from BL HAQ-DI MCID (change ≥0.22 from BL) Fatigue change from BL Pain VAS change from BL SF-36 PCS change from BL SF-36 MCS change from BL (52 weeks)	55% vs. 39% -1.02 vs. -0.72 88% vs. 78% -29.6 vs. -19.7 -41.9 vs. -31.4 13.7 vs. 10.7 6.78 vs. 6.1	<0.0004 <0.001 0.006 <0.001 <0.001 0.003 NS
St Clair *et al*. 2004 (ERA) (24)	0.9 years	IFN 3 mg/kg + MTX (359) IFN 6 mg/kg + MTX (363) MTX (282)	HAQ MCID (change ≥0.22 from BL) (54 weeks)	76% vs. 76% vs. 65%	0.003 0.004
van der Kooij *et al*. 2009 (BeSt) (25)	2 weeks*	1: Sequential monotherapy[a] 2: Step-up combination therapy[b] 3: Initial combination therapy with prednisone[c] 4: Initial combination therapy with IFN[d]	MACTAR (1 year) SF-36 PCS change from BL SF-36 MCS change from BL Pain VAS change from BL Disease activity VAS change from BL Global health VAS change from BL (2 years)	15.2 vs. 16.3 vs. 16.9 vs. 19.3 11.9 vs. 12.3 vs. 12.3 vs. 12.7 4.3 vs. 4.6 vs. 4.6 vs. 4.0 -38.2 vs. -27.3 vs. -26.9 vs. -32.6 -33.2 vs. -33.0 vs. -31.5 vs. -39.0 -26.45 vs. -25.6 vs. -23.9 vs. -31.8	0.02 1vs.4 0.95 0.97 0.33 0.19 0.1
Breedveld *et al*. 2006; Kimel *et al*.2008 (PREMIER) (26, 27)	0.7 years	ADA + MTX (268) ADA (274) MTX (257)	HAQ MCID (change ≥0.22 from BL) SF-36 PCS (2 years)	72% vs. 58% vs. 63% 47.5 vs. 48.3 (US population norms)	<0.05 0.25
Bejarano *et al*. 2008 (PROWD) (28)	0.8 years	ADA + MTX (75) MTX (73)	HAQ-DI change from BL RAQoL change from BL (56 weeks)	-0.7 vs. -0.4 -7.6 vs. -4.7	0.005 0.027
Established RA					
Schiff *et al*. 2006 (30)	>3 years	ETN ETN + MTX	HAQ-DI MCID (change ≥0.22 from BL) (48 months)	58% vs. 71%	NA
Farahani *et al*. 2006 (31)	12 years	ETN (223) No ETN (208)	HAQ score change from BL SF-36 PCS change from BL SF-36 MCS change from BL (1 year)	-0.4 vs. -0.2 4.5 vs. 0.6 2.2 vs. 2.0	0.04 0.005 0.9
Virkki *et al*. 2008 (32)		IFN	HAQ score ≥0.25 change from BL	>66% patients	
Strand and Singh 2007; Torrance *et al*. 2004; (ARMADA, DE019) (20, 33)	11 years	Study 1 ADA + MTX (64) MTX (57) Study 2 ADA + MTX (191) MTX (187)	HUI3 change from BL (Study 1, 24 weeks; Study 2, 52 weeks) HAQ-DI change from BL (6 months) SF-36 PCS change from BL (6 months)	Study 1: 0.22 vs. 0.04 Study 2: 0.21 vs. 0.07 Study 1: -0.62 vs. -0.27 Study 2: -0.56 vs. -0.24 Study 1: 9.3 vs. 2.6 Study 2: NA	0.002 <0.0001 NA ≤0.001 NA
Heiberg *et al*. 2006 (NOR-DMARD register) (34)	13 years	ADA + MTX (99) ADA (84)	SF-36 domains, change from BL Physical functioning Role physical Bodily pain Vitality Social function Role emotional Mental health General health (6 months)	 9.9 vs. 2.7 22.6 vs. 14.1 14.0 vs. 8.5 12.3 vs. 1.9 14.3 vs. 4.9 16.7 vs. -1.4 8.6 vs. -2.2 7.5 vs. -0.05	 0.08 0.21 0.14 0.01 0.08 0.03 0.0001 0.02

***Table I** continues on next page*

Reference	Disease duration (mean)	Treatment arms (n) active and control	Outcome measures (mean) (time point)	Results active *vs*. control	*p*-value
Burmester *et al*. 2007 (ReAct) (35)	11 years	ADA + other DMARDs (4879) ADA (1731)	HAQ-DI change from BL (12 weeks)	-0.54 vs. -0.47	–
Mittendorf *et al*. 2007 (DE033) (36)	12 years	ADA (505)	FACIT-F change from BL at week 12	7.2	–
			HUI3 change from BL	0.11	
			SF-36 change from BL[e]		
			Physical functioning	0.87	
			Role physical	-1.07	
			Bodily pain	0.62	
			General health	-0.29	
			Vitality	0.33	
			Social functioning	-0.12	
			Role emotional	-2.15	
			Mental health	-0.9	
			PCS	-0.48	
			MCS	-2.03	
			(3 years)		
Keystone *et al*. 2009 (GO-FORWARD) (37)	6 years	GOL 50 mg + MTX (89) GOL 100 mg + MTX (89) GOL 100 mg (133) MTX (133)	HAQ-DI change from BL	-0.38 vs. -0.5 vs. -0.13 vs. -0.13	<0.001; 0.24[f]
			HAQ-DI change ≥0.25	68.2% vs. 72.1% vs. 45.3%	<0.001; 0.28
			(24 weeks)	vs. 38.6%	
Keystone *et al*. 2008; Strand *et al*. 2008 (RAPID 1) (38, 39)	6 years	CZP 200 mg + MTX (393) CZP 400 mg + MTX (390) MTX (199)	HAQ-DI change from BL	-0.60 vs. -0.63 vs. -0.18	<0.001
			SF-36 change from BL		
			Physical functioning	16.7 vs. 17.9 vs. 1.7	<0.001
			Role physical	26.9 vs. 29.1 vs. 8.1	<0.001
			Bodily pain	23.5 vs. 26.2 vs. 6.8	<0.001
			General health	13.0 vs. 13.0 vs. 3.1	<0.001
			Vitality	15.1 vs. 15.6 vs. 4.5	<0.001
			Social functioning	18.5 vs. 18.6 vs. 3.2	<0.001
			Role emotional	23.9 vs. 26.1 vs. 7.1	<0.001
			Mental health	10.6 vs. 9.9 vs. 3.0	<0.001
			PCS	7.8 vs. 8.6 vs. 1.7	<0.001
			MCS	6.4 vs. 6.4 vs. 2.1	<0.001
			(52 weeks)		
Smolen *et al*. 2009; Strand *et al*. 2008 (RAPID 2) (39, 40)	6 years	CZP 200 mg + MTX (246) CZP 400 mg + MTX (246) MTX (127)	HAQ-DI change from BL	-0.5 vs. -0.5 vs. -0.14	<0.001
			HAQ-DI MCID (change ≥0.22 from BL)	57% vs. 53% vs. 11%	<0.001
			SF-36 change from BL		
			Physical functioning	12.1 vs. 12.4 vs. 0.61	<0.001
			Role physical	18.8 vs. 18.1 vs. 5.1	<0.001
			Bodily pain	17.3 vs. 19.1 vs. 5.7	<0.001
			General health	11.2 vs. 12.1 vs. 3.4	<0.001
			Vitality	11.8 vs. 13.3 vs. 2.1	<0.001
			Social functioning	14.6 vs. 15.6 vs. 3.9	<0.001
			Role emotional	20.5 vs. 16.5 vs. 4.2	<0.001
			Mental health	10.6 vs. 13.2 vs. 4.1	<0.001
			PCS	5.2 vs. 5.5 vs. 0.9	<0.001
			MCS	6.1 vs. 6.3 vs. 1.6	<0.001
			(24 weeks)		
Fleischmann *et al*. 2009; Strand *et al*. 2007 (FAST4WARD) (41, 42)	10 years	CZP 400 mg (111) PBO (109)	HAQ-DI change from BL	-0.36 vs. -0.13	<0.001
			HAQ-DI MCID (change ≥0.22 from BL)	49% vs. 12%	<0.001
			Pain VAS change from BL	-20.6 vs. 1.7	<0.001
			Pain MCID (change ≥10 from BL)	47% vs. 17%	<0.001
			FAS change from BL	-1.69 vs. -0.27	<0.001
			FAS MCID (change ≥1 from BL)	46% vs. 17%	<0.001
			SF-36 MCID (change from BL ≥5 in domains and ≥2.5 in PCS and MCS)		
			Physical functioning	43% vs. 11%	<0.001
			Role physical	38% vs. 11%	<0.001
			Bodily pain	53% vs. 13%	<0.001
			General health	41% vs. 12%	<0.001
			Vitality	45% vs. 11%	<0.001
			Social functioning	48% vs. 15%	<0.001
			Role emotional	20% vs. 6%	0.002
			Mental health	36% vs. 6%	<0.001
			PCS	47% vs. 16%	<0.001
			MCS	35% vs. 8%	<0.001
			(24 weeks)		

*Median time from diagnosis to inclusion
[a]MTX, then SSA, then LEF, then MTX + INF; [b]MTX, then MTX + SSA, then MTX + SSA + HCQ, then MTX + SSA + HCQ + prednisone, then MTX + INF; [c]MTX + SSA +prednisone (tapered from 60 to 7.5 mg/day), then MTX + cyclosporine A + prednisone 7.5 mg/day, then MTX + INF; [d]MTX + INF, then SSA, then LEF; [e]Numbers calculated from Table II in Mittendorf *et al* .2007; [f]Active versus MTX group.
ETN: etanercept; MTX: methotrexate; HAQ-DI: Health Assessment Questionnaire Disability Index; BL: baseline; MCID: minimum clinically important difference; VAS: visual analogue scale; SF-36: Short-Form 36; PCS: physical component summary; MCS: mental component summary; IFN: infliximab; MACTAR: McMaster Toronto Arthritis patient preference questionnaire; ADA: adalimumab; RAQoL: rheumatoid arthritis-related quality of life; HUI3, Health Utilities Index Mark 3; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; GOL: golimumab; CZP: certolizumab pegol; SSA: sulfasalazine; LEF: leflunomide; HCQ: hydroxychloroquine; DMARDs: disease-modifying anti-rheumatic drugs; FAS: fatigue assessment scale; NS = not significant.

52 weeks, compared with MTX alone (33). Similarly, in a 6-month study, adalimumab plus MTX improved some mental and general HRQoL outcomes by 3 months compared with adalimumab alone, although these differences were not observed in physical, pain, or social domains (34). In a larger study, however, patients with RA treated with adalimumab plus one or more concomitant DMARDs showed greater improvements in disability over 12 weeks than those given adalimumab alone (35). Adalimumab monotherapy did improve patients' perceptions of fatigue (by 12 weeks) and HRQoL (by 12 weeks) on a number of measures in a longer-term study of 3 years (36). In addition to these TNF inhibitors, golimumab has been shown to improve disability in a 24-week study when combined with MTX but not as monotherapy, with improvements seen by week 14 compared with placebo plus MTX (37).

Certolizumab pegol is the most recently available TNF inhibitor approved for treatment of adult patients with moderately to severely active RA. In addition to demonstrating significant clinical efficacy in the treatment of RA as either monotherapy or in combination with MTX (38, 40, 41), it has been shown to significantly improve multiple aspects of HRQoL in patients with long-term RA (Table I). Significant and clinically meaningful improvements in physical function (measured by HAQ-DI ≥0.22) and relief of pain (by 100-mm visual analog scale [VAS] and modified Brief Pain Inventory) have been reported as early as 1 week after initiation of therapy, as monotherapy or in combination with MTX (38-41, 43). Patients treated with certolizumab pegol also report significantly and clinically meaningful reductions in fatigue (41), and improvement in both physical and mental summary and domain scores of SF-36 as early as the first assessment at week 12 (39-42) (Fig. 1).

Taken together, these data demonstrate that the TNF inhibitors provide clinically meaningful improvements in physical function as well as HRQoL, and provide relief of pain and fatigue. In addition, onset of benefits are rapid and patients can achieve significant improvements as early as week 1 of therapy, recently demonstrated by data from phase 3 randomised controlled trials with certolizumab pegol.

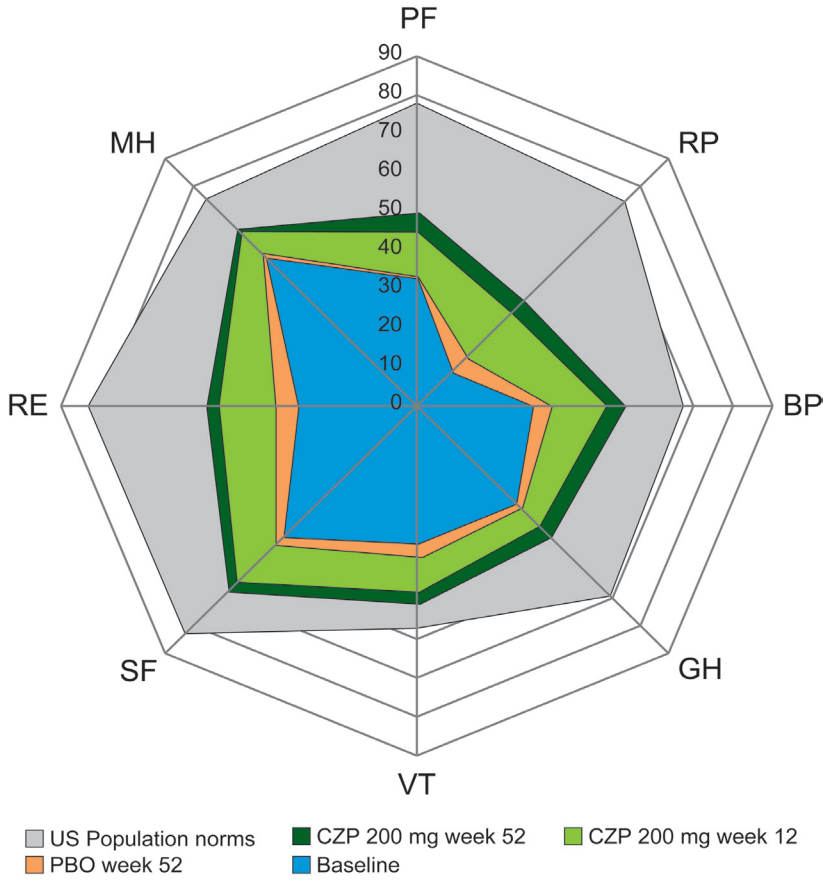

Fig. 1. Spydergram of SF-36 domains at baseline and following treatment with certolizumab pegol 200 mg in the RAPID 1 clinical trial (ITT population, LOCF). CZP: certolizumab pegol; PBO: placebo. Physical domains: Physical Function (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH). Mental domains: Vitality (VT), Social Function (SF), Role Emotional (RE), Mental Health (MH). Domain scores are plotted from 0 (worst) at the center to 100 (best) at the outside; demarcations along axes of the domains present changes of 10 points, representing 1 – 2 times MCID. From STRAND V *et al*., *Arthritis Res Ther* 2009; 11: R170 (12 November 2009).

Impact of RA on productivity and economic loss

Decrements in HRQoL, especially reduced physical function, are associated with an increased probability of no longer working, or engaging in housework, absence from work due to RA-associated sickness (absenteeism), and reduced productivity while at work or in the home (presenteeism) (44), all of which have personal and economic consequences for the patient. Pain and fatigue also affect patients' ability to attend work and to perform paid and unpaid work and household activities (45-47). In addition, patients report that active disease significantly impacts their private lives, work/social responsibilities, and their self-image (48); RA also impairs patients' ability to engage in family, social, and leisure activities (49-51). As a result, patients often have to seek additional support to meet their individual role obligations. This may include assistance from family members or hired household personnel, or asking their employers to be more flexible in terms of attendance/performance. They may also require ergonomic work-place modifications. All of these factors combine as additional personal financial burdens reflecting the impact of RA.

In a Finnish study conducted in 2002 among patients with recent onset RA, the mean loss of work productivity per patient-year (calculated from data on job absenteeism for sickness and income) was €6477 for women and €8443 for men (52). Costs of care and

hired assistance in the home are also important contributors to patients' financial burden. In a study of the economic consequences associated with RA, 59% patients reported needing unpaid and 27% needed paid help in a 6-month period (53). The annual cost associated with lost time from work in this Canadian study (including paid assistance) was US$ 3,458 per patient. Costs are also borne by care givers, especially family members, and costs to support persons due to their own time lost from work were US$ 88 for a year. This figure is likely to be an underestimate, however, due to difficulties in assessing productivity losses ascribed to alterations in presenteeism.

A number of studies have assessed the economic impact of RA in early disease. Even early in the course of disease, considerable direct and indirect costs are incurred. A study of costs associated with RA in the US during the first year following diagnosis reported that annual costs attributable to RA were US$ 5,760 (in 1994 US$) (54). Furthermore, direct and indirect costs were not dissimilar (US$ 2,400 and US$ 3,372, respectively). Patients in this study reported a work disability rate of 18% due to their RA; an average of 3.8 days lost per month. Similar findings were observed in a Swedish study of RA patients during their first year after diagnosis, although average indirect costs were 2-3 times higher than average direct costs (US$ 11,000 compared with US$ 5,000, respectively) (55). Increased sick leave ascribed to RA contributed to these high indirect costs, accounting for an average of 170 sick-leave days in that first year following diagnosis. Increased costs were associated with poorer physical functioning, and higher self-reported pain scores.

In longer-duration disease, costs are even higher. Total annual costs in a Canadian study of patients with RA were equivalent to US$ 9,348 (year 2000 US$ equivalent), of which 55% were direct costs (53). In Germany, in a study of gainfully employed patients and recipients of RA-related retirement payments with a mean RA disease duration of 8 years, costs related to decreased productivity exceeded direct costs (56). Total direct costs were €3,815 (approx. US$ 5,500); specifically RA-related costs €2,312 (approx. US$ 3,000) per patient-year. The profound impact of disease on employment was reflected in that 30% of patients retired prematurely due to RA-related work disability, and incurred costs of €8,358 (approx. US$ 12,000) per retired patient-year. Among those patients who continued to be gainfully employed, sick leave costs amounted to €2,835 (approx. US$ 4,000) per employed patient-year. Productivity loss was associated with more severe disease, both in terms of musculoskeletal symptoms and depression.

Impact of treatment on productivity

Due to the effect of RA on normal participation at work, in the home, and socially, treatment-related improvements in productivity are also important for patients. In early RA, studies with etanercept, infliximab, and adalimumab have shown improvements in work productivity (Table II) (23, 28, 57, 58).

In a 52-week study of etanercept plus MTX compared with MTX alone, fewer patients in the etanercept group (9%) stopped working since their prior visit than in the MTX group (24%; $p<0.004$) (23). Similarly, employed patients treated with infliximab plus MTX were less likely to become unemployable or to lose work days, and were more likely to improve their employability over 54 weeks, compared to those given placebo plus MTX (57). Combination therapy with adalimumab and MTX over 2 years has also resulted in fewer work days missed (for both paid workers and homemakers), and improved productivity at both work and home, than MTX alone (58). Adalimumab plus MTX also reduced job loss and improved productivity compared with placebo plus MTX in a shorter study, of 56 weeks, and also improved work instability outcomes (28). Although there was no difference between the two groups in the primary end point of this latter study (job loss/imminent job loss at or after week 16), adalimumab plus MTX was more beneficial in terms of this outcome than placebo plus MTX over 56 weeks.

In established RA, more patients treated with etanercept maintained their employment (work for pay or profit) and fewer lost their employment than those who did not receive etanercept as part of their therapy (59). Employed patients treated with etanercept also worked for longer hours than those not receiving this agent. However, the assessment tools used in these studies have a number of limitations, including day-to-day variability, and some studies report "normalised" domain scores that limit the applicability of data (20, 60). Recently, a new tool for the assessment of productivity at paid work and in the home, the novel Work Productivity Survey-RA, has been validated (61). This instrument, which is specifically designed for RA, uses a total of nine questions to assess employment status, work productivity outside the home and within the home, as well as family/social/leisure activities. Using this new tool, patients treated with certolizumab pegol reported improvements in productivity both at work and in the home (Table II) (62). In an analysis of data from two clinical trials, treatment with certolizumab pegol plus MTX significantly reduced work absenteeism (defined as work days missed due to RA-associated illness), presenteeism (defined as days with productivity reduced by ≥50%), and the rate of RA interference with work productivity. In addition, there was a significant reduction in number of household days lost, household days with productivity reduced ≥50%, requirements for outside help, and interference in household productivity, and in days lost due to RA for participation in family, social, and leisure activities with certolizumab pegol plus MTX treatment. Significant improvements in most measures were observed with certolizumab pegol as early as week 4, and were maintained for up to 1 year of therapy. The home productivity data with certolizumab pegol are noteworthy since information on these outcomes with other TNF inhibitors for RA is limited because productivity measures of daily activities within the home and participation in social activities were not included in clinical trials of these agents.

Table II. Improvements in productivity outcomes with TNF inhibitors in early and established RA.

Reference	Disease duration (mean)	Treatment arms (n) active and control	Outcome measures (mean) (time point)	Results active *vs*. control	
Early RA					
Emery *et al*. 2008 (COMET) (23)	0.8 years	ETN + MTX (265) MTX (263)	Stopping work outside home at least once (52 weeks)	9% vs. 24%	p=0.004
Smolen *et al*. 2006 (ASPIRE) (57)	0.9 years	IFN + MTX* (722) MTX (282)	Become unemployable Lost work days Improved employability (54 weeks)	8% vs. 14% 21% vs. 33% 8% vs. 2%	p=0.05 p=0.01 p<0.001
van Vollenhoven *et al*. 2007 (58)	0.5 years	ADA + MTX (219) MTX (214)	Lost work days (paid workers) Lost work days (homemakers) Decrease in VAS-work scores** (paid workers) Decrease in VAS-work scores ** (homemakers) (2 years)	15 vs. 26 8 vs. 14 -36 vs. -27 -36 vs. -24	p<0.001 p<0.001 p=0.01 p=0.0007
Bejarano *et al*. 2008 (28)	0.8 years	ADA + MTX (75) MTX (73)	Job loss/imminent job loss at or after week 16 Job loss/imminent job loss over 56 weeks Change in Work Instability Scale from BL Work time lost (56 weeks)	16% vs. 27% 19% vs. 40% -8.1 vs. -5.4 9% vs. 18%	p=0.092 p=0.005 p=0.025 p=0.038
Established RA					
Yelin *et al*. 2003 (59)	16 years	ETN (259) No ETN (238)	Lost employment*** Maintained employment*** (between diagnosis and study year) Hours worked per week† (in the year prior to latest interview)	22% vs. 34% 55% vs. 41% 26.8 vs. 21.4	– – p<0.05
Kavanaugh *et al*. 2009 (RAPID 1, RAPID 2) (62)	6 years	Study 1 CZP 200 mg + MTX (393) CZP 400 mg + MTX (390) MTX (199)	Work days missed Days with work productivity reduced ≥50% Rate of interference with work productivity Household work days missed Days with household work productivity reduced ≥50% Days with outside hired help Rate of interference with household productivity Decrease in days lost of family, social and leisure activities (in 1 month at end of 52-week study)	1.0 vs. 1.4 vs. 4.5 2.1 vs. 2.1 vs. 4.4 2.4 vs. 2.4 vs. 5.2 2.4 vs. 2.8 vs. 7.2 4.2 vs. 3.8 vs. 7.3 1.9 vs. 1.7 vs. 4.0 3.3 vs. 3.1 vs. 5.6 1.6 vs. 1.6 vs. 3.7	p≤0.05 p≤0.05 p≤0.05 p≤0.05 p≤0.05 p≤0.05 p≤0.05 p≤0.05
		Study 2 CZP 200 mg + MTX (246) CZP 400 mg + MTX (246) MTX (127)	Work days missed Days with work productivity reduced ≥50% Rate of interference with work productivity Household work days missed Days with household work productivity reduced ≥50% Days with outside hired help Rate of interference with household productivity Decrease in days lost of family, social and leisure activities (per month over 24 weeks)	1.3 vs. 1.0 vs. 2.5 3.1 vs. 2.3 vs. 9.3 3.0 vs. 2.5 vs. 5.2 2.7 vs. 2.7 vs. 6.5 5.2 vs. 4.0 vs. 9.2 1.3 vs. 1.8 vs. 4.8 3.8 vs. 3.3 vs. 5.8 1.4 vs. 1.3 vs. 3.8	NS p≤0.05 p≤0.05 p≤0.05 p≤0.05 p≤0.05 p≤0.05 p≤0.05

*IFN 3 mg/kg and INF 6 mg/kg combined; **Change from baseline in VAS-work scores; ***Work for pay or profit; †Adjusted for demographic and health characteristics, and occupation and industry, at time of diagnosis.

Thus, the TNF inhibitors have been shown to improve productivity, with fewer patients having to stop work and more patients reporting improved productivity at work within and outside of the home, and to provide benefits related to increased participation in family and social activities. In general, patients with early RA are more likely to show improved employment outcomes after treatment than those with long-standing RA; intervention as early as possible in the disease course thus maximises an individual patient's employment potential (63).

Summary

RA has significant detrimental effects on multiple aspects of patients' HRQoL and is associated with substantial health care resource utilisation as well as a significant economic burden for both patients and society. Treatment with TNF inhibitors and other agents improves outcomes of pain, fatigue, and physical and mental well-being. These agents also improve productivity at work. The most recently available agent in this class, certolizumab pegol, has been shown to improve quality of

life-related outcomes as early as 1 week after starting treatment, and to improve productivity in the home as well as participation in social and leisure activities. These benefits have important implications not only for patients, but also for their families, friends, and society overall.

The long-term socioeconomic burden of disease, and its alleviation through treatment, should, therefore, be considered when assessing TNF inhibitor therapy options and their risk:benefit ratio. Overall social productivity/participation outcomes should also be included as outcomes in clinical trials and daily practice.

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