

# Can anti-TNF agents protect against rheumatoid arthritis-associated work disability?

The purpose of this perspective is to summarize recent literature on the effect of anti-TNF agents on work disability in patients with rheumatoid arthritis (RA). The current literature shows that the prevalence of work disability, including work cessation, sick leave and any other restriction in the work status, among patients with RA is substantial. In recent studies a trend towards a decline in work disability in RA is seen, which is considered to reflect improvements in drug treatment over the past decades. Overall, the number of studies on the effect of anti-TNF agents on work disability in RA is limited, with the majority being observational or having a nonrandomized design. In randomized controlled trials, in general a positive effect of anti-TNF agents on work disability in early RA was seen. Depending on the way productivity is valued, it was found that savings on productivity may compensate for the high costs of anti-TNF agents in early RA. In the future, more prospective studies on anti-TNF agents and work disability, including sufficient numbers of patients with early RA and a long-term follow-up, are needed. Measurement of work disability should not only include job loss or absenteeism, but also reduced productivity while at work. In addition, the impact of anti-TNF on the value of unpaid work should be studied.

**KEYWORDS:** adalimumab ■ economic evaluation ■ employment ■ etanercept  
■ infliximab ■ productivity costs ■ rheumatoid arthritis ■ TNF antagonist  
■ work disability

Over the past years, work disability has been increasingly recognized as a major consequence of rheumatoid arthritis (RA) [1], and has become a generally accepted outcome measure in clinical studies [2]. Work disability in rheumatic conditions is usually defined as complete or partial work cessation due to the disease prior to the age of retirement [3]. However, in some studies a broader definition is used, also concerning any restriction in the work status, such as absenteeism or sick leave, or any reduction in productivity while present at work (so called presenteeism). Apart from work disability, productivity loss is also used as an umbrella term for work cessation, sick leave/absenteeism or reduction in productivity while present at work.

This perspective summarizes the recent literature on work disability in RA and the impact of anti-TNF agents on RA-related work disability, including health economic issues. Moreover, future developments in this area of research are discussed.

## Epidemiology of work disability & problems encountered in the working situation in RA

### ■ Work cessation

The epidemiology of work disability in chronic arthritis has been the subject of many studies.

With respect to work cessation, rates of complete and permanent job loss of 50% after 10 years of disease duration are often quoted [4]. Recent studies point into the direction of a decline, with the prevalence of premature work cessation after 10 years reported to be 35% [5]. Allaire *et al.* found the prevalence of any premature work cessation to be 23% in subjects with 1–3 years RA duration, 35% in those with 10 years, and 51% in those with at least 25 years RA duration [4]. Arthritis-attributed work cessation was 14, 29 and 42%, after 1–3, 10 and 25 years of disease duration, respectively. Over a period of 4 years, 39% of subjects who stopped working at least once, later returned to work.

The severity of the disease and functional impairments, sociodemographic and psychological factors, job characteristics and macro-economic factors have been reported as being decisive for maintaining employment in RA [6–8]. In a recent study using a large RA cohort, older age, lower income, fewer working hours and preference not to work were the risk factors for loss of employment [9]. In that study, the impact of disease factors was limited to subjects aged at least 56 years, and job physical demand was found to have little impact.

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### ■ Sick leave or absenteeism

At present, the interest in sick leave or absenteeism, which is considered to precede permanent work disability in chronic arthritis, is increasing. In a systematic review on productivity loss in RA, the proportions of patients experiencing absenteeism or short-term sick leave was found to vary from 22 to 76% (median 54%) in the previous 6 months and from 36 to 84% (median 66%) in the previous 12 months [10]. In a recent study in patients with early arthritis, 41% reported sick leave due to arthritis in the 12 months preceding entry into an early arthritis clinic, and 26% in the subsequent 12 months of follow-up [11]. In that study, sick leave in the 12 months before study entry appeared to be the most important predictor of the institution or increase in a work disability pension (odds ratio [OR]: 16.1; 95% CI: 1.8–142.8). Geuskens *et al.* found that sick leave was reported by 54 (26%) of 210 patients with inflammatory arthritis with a duration of less than 12 months (48 of whom had RA) in the past 6 months [12]. In that study, pain, poor physical functioning, low control over planning and pacing of activities within the job were related to increased sick leave.

### ■ Problems or reduction in productivity while present at work

A number of challenges experienced at work in RA patients have previously been identified [13,14], including pain, fatigue and physical limitations, travel to work, lack of support from employer, colleagues or family, and lack of specific adaptations to the work place. Recently, a chronic illness job strain survey showed that employed individuals with osteoarthritis or inflammatory arthritis reported concerns about future uncertainty, accepting changes in life, balancing multiple roles and dealing with symptoms of arthritis to be the most stressful [15]. From a qualitative study among adults with inflammatory arthritis [16], it was concluded that fatigue; invisibility, fluctuation and unpredictability of arthritis; complexity of interpersonal relationships at work and reluctance to disclose or draw attention to arthritis; barriers to using available supports and requesting job accommodations; loss of self-efficacy at work; and many emotional challenges were important problems faced at work by patients with chronic arthritis.

In a recent study among 120 employed patients with RA [17], 90 completed the RA-Work Instability Scale (RA-WIS) [18,19]. The RA-WIS is a screening tool for work instability: the consequence of a mismatch between the individual's

functional ability and his or her work tasks that threatens the individual's continued employment if not resolved [18]. In this study it was found that functional impairment and disease activity significantly and independently contributed to patient-perceived work instability.

### Anti-TNF & work disability

The question of whether optimal treatment with DMARDs, and in particular new biological therapies, will result in better work prospects for patients with RA has been addressed in a number of studies published over the past few years.

With respect to DMARDs, it was found in patients with early RA that aggressive initial treatment with a combination of DMARDs had a positive effect on the cumulative duration of work disability, in particular on sick leave over 5 years [20,21].

Compared with conventional DMARDs, therapeutic strategies including anti-TNF therapy have been shown to be more effective in controlling disease symptoms. Anti-TNF agents have also been shown to improve disability and slow radiographic progression. Whether treatment with these agents will result in better work prospects for patients with RA remains to a large extent unknown [22,23]. Studies on the impact of anti-TNF therapy on work disability in RA are summarized in TABLE 1 [24–33]. With respect to the description of the outcomes of these studies, a distinction will be made according to:

- Employment status (being employed or not, and number of hours being employed);
- Sick leave or absenteeism;
- Problems encountered or reduction in productivity while present at work.

Yelin *et al.* studied the association between etanercept use and employment outcomes among 497 patients with RA of working ages [24]. Specifically, a comparison was made between the working status of the patients who were employed at the time of diagnosis and had either been in clinical trials of etanercept or had not been taking etanercept.

With respect to employment status, 75% of RA patients who did not take etanercept and 77% of those who did take that medication were employed. At the time the study was conducted (in 1999), among those employed at diagnosis, 55% of the patients in the group who did not take etanercept and 71% of the patients in the group who did take the medication were employed (a difference of 16%). After

Table 1. Characteristics and outcomes of clinical studies on anti-TNF agents and work disability.

Study	No. of patients	Duration of RA (years)	Study design	Anti-TNF treatment and control condition(s)	Duration of follow-up (years)	Authors' conclusions	Ref.
Yelin <i>et al.</i> (2003)	497	At follow-up: 15.7 ± 8.7	Comparison of an observational study and a clinical trial	Etanercept (n = 238) versus no etanercept (n = 259)	From diagnosis to 1999: 14.0 ± 8.3 (etanercept) 17.2 ± 8.8 (no etanercept)	Among RA patients who were employed at baseline, having been in etanercept clinical trials was associated with higher employment rates in 1999 and a greater number of hours per week of work in that year	[24]
Smolen <i>et al.</i> (2006)	856	At baseline: <3 years	RCT	MTX plus infliximab (n = 621) versus MTX plus placebo (n = 235)	54 weeks	The actual employment rates among patients in the two treatment groups were not different. However, patients with early RA who were treated with MTX plus infliximab had a higher probability of maintaining their employability compared with those who were treated with MTX alone	[25]
Laas <i>et al.</i> (2006)	96 (65 with RA); 51 working at baseline	16 (range 3–43) for total group of 96	Observational	Infliximab	12 months	Work disability costs failed to show a substantial decrease after 1 year of treatment with infliximab in patients with long-standing aggressive arthritis	[26]
Farahani <i>et al.</i> (2006)	431; 223 etanercept/208 no etanercept	12.5, SD: 9.2 etanercept/12.3, SD: 9.7 control	Observational comparison of two groups	Etanercept/no etanercept	12 months	Etanercept can effectively improve work disability during the first 6 months of use	[27]
Wolfe <i>et al.</i> (2007)	3886	12.5 (SD: 9.5); all anti-TNF/14.1 (SD: 10.8); no anti-TNF	Observational comparison of two groups	All anti-TNF agents (n = 1986) versus no anti-TNF (n = 1900)	From diagnosis to analysis: 12.8 years	No positive effect of anti-TNF therapy on the risk of work disability was seen	[28]
Allaire <i>et al.</i> (2008)	953; 231 cases/722 controls	15 ± 9.9 (cases) and 13 ± 9.4 (controls)	Nested, matched case-control study	All anti-TNF agents	18 months	Anti-TNF agents did not protect against work disability in the main analyses. In stratified analyses, their use was protective among subjects with shorter disease duration	[29]
Bejarano <i>et al.</i> (2008)	148	≤2	RCT	MTX plus adalimumab (n = 75) versus MTX plus placebo (n = 73)	56 weeks	Adalimumab plus MTX reduced job loss and improved productivity in early RA when compared with MTX alone	[30]
Halpern <i>et al.</i> (2008)	338 working at baseline	10.5, adalimumab/10.7 DMARD	Observational comparison of two groups	Adalimumab (n = 158) versus DMARD (n = 180)	24 months	Patients with RA receiving adalimumab experienced significantly longer periods of work and continuous employment than did those receiving DMARDs	[31]
van den Hout <i>et al.</i> (2009)	508	≤2	RCT	Initial combination therapy with infliximab versus 3 treatment strategies initially without anti-TNF agents	24 months	Worked hours were highest for patients with initial combination therapy with infliximab. Depending on the extent to which productivity is valued, infliximab costs could be largely compensated for by savings on productivity	[32]
Hoving <i>et al.</i> (2009)	59; 26 with paid job	10.7 (SD: 8.9)	Observational	Adalimumab	6 months	A 6-month course of adalimumab improved work ability	[33]

MTX: Methotrexate; RA: Rheumatoid arthritis; RCT: Randomized controlled trials; SD: Standard deviation.

adjustment for demographics, overall health status, duration of RA, RA status and occupation and industry, the difference widened to 20%. Among all who were employed at the time of diagnosis, those from the etanercept clinical trials worked an average of 5.4 more hours per week in 1999; after adjustment, the etanercept group worked 7.4 more hours per week.

Smolen *et al.* evaluated the impact of TNF blockade on the employment status of patients with early-stage RA who participated in the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) [25]. In this study, patients who were methotrexate (MTX) naive, had active RA, and had a history of persistent synovitis (for at least 3 months but no longer than 3 years from the date of diagnosis), began receiving MTX therapy and were randomly assigned to receive either infliximab or placebo infusions (with different randomization weights). A total of 621 patients in the MTX plus infliximab group and 235 patients in the MTX plus placebo group were aged 64 years or less. In addition to employment, employability was measured, with patients categorized as employable (being either employed or being unemployed, but feeling well enough to work if a job were available) or unemployable (being unemployed and feeling unable to work despite job availability). Moreover, for each patient the number of days missed at work because of their arthritis in the past period was measured.

At week 54, the change in actual employment status was not significantly different between patients receiving MTX plus infliximab and those receiving MTX plus placebo (net employment loss 0.5 vs 1.3%;  $p > 0.5$ ).

However, self-reported employability did show a difference: the proportion of patients whose status changed from employable at baseline to unemployable at week 54 was smaller in the group receiving MTX plus infliximab compared with that in the group receiving MTX alone (8 vs 14%;  $p = 0.05$ ). Overall, the proportion of patients who considered themselves employable at week 54 was greater among treatment responders (based on the ACR 20% response criteria) than among nonresponders, both in the MTX plus placebo and the MTX plus infliximab groups.

The proportion of employed patients who lost one or more work days during the trial was smaller in the MTX plus infliximab group (21.1%) than in the MTX-alone group (33.4%) ( $p = 0.010$ ).

A comparison of work disability costs in the 1-year period before and the 1-year period after the institution of infliximab treatment was made by Laas *et al.* [26]. In this Finnish study, 96 patients, with a mean disease duration of 16 years, were included in total. A total of 51 of these patients were available for the work force at baseline. Work disability costs included the costs associated with the number of days off work, rehabilitation allowances and disability pensions, and thus reflect both employment status and absenteeism.

Mean work disability costs were €7166 (95% CI: 4327–12047) in the year before the start of infliximab treatment, with the mean change being -€130 (95% CI: -1268–1072) in the year thereafter.

The mean number of days off work on short-term sick leave or rehabilitation allowance before treatment with infliximab was 121, and this increased to 141 in the second measurement period.

Farahani *et al.* compared disease state, functional class, quality of life and work disability among patients requesting etanercept therapy, stratified into treatment and control group based upon individual accessibility in obtaining the drug [27]. At baseline, of the 223 patients in the treatment group and the 208 patients in the control group, 35.8 and 33.1% were gainfully employed, respectively.

The outcome regarding working status was expressed in terms of absenteeism and 'down' days (the days the patient did not feel well and needed rest due to RA).

Concerning absenteeism, at 6 months in employed patients, the accumulated number of missed days from work was significantly less for the treatment group than for the control group (2.5 [standard deviation (SD): 7] and 7.8 [SD: 19],  $p = 0.03$ ), whereas at 12 months the difference was no longer significant. Moreover, among employed patients there were fewer 'down' days in the treatment group (11.8 days) than in the control group (28.0 days) at 6 months ( $p < 0.002$ ), but not at 12 months.

Wolfe *et al.* examined the effect of anti-TNF therapy on work disability using data from the National Databank for Rheumatic Diseases, in which participants are recruited on an ongoing basis from the practices of US rheumatologists and followed prospectively with semi-annual questionnaires [28]. They studied 3886 subjects who were employed at study entry, of whom 1986 received and 1900 did not receive anti-TNF therapy. At follow-up, employment status



was determined according to the patients' self-report (employed, disabled with receipt of Social Security disability benefits or self-reported work disability).

After adjustment for demographics, RA severity and co-morbidity, anti-TNF therapy was not associated with Social Security disability (relative risk [RR]: 1.2; 95% CI: 0.8–1.8) but was associated with an increased risk of self-reported disability (RR: 1.6; 95% CI: 1.1–2.4).

Allaire *et al.* studied 953 patients with RA from a USA cohort using a nested, matched, case–control approach [29]. All subjects were employed at baseline and aged less than 65 years at last follow-up. Their mean age was 51 years; nearly half (48%) used an anti-TNF agent at baseline.

Employment status (defined as performing any amount of employment work) was the main outcome measure in this study. In the main analysis, anti-TNF use did not protect against any or RA-attributed employment loss (OR: 0.9; 95% CI: 0.5–1.5). However, a protective effect was found in a subgroup of users with RA and a disease duration of less than 11 years (OR: 0.4; 95% CI: 0.2–0.9).

Bejarano *et al.* compared work disability in 148 patients with early RA ( $\leq 2$  years) receiving MTX plus adalimumab ( $n = 75$ ) or MTX plus placebo ( $n = 73$ ) [30]. The primary end point of the study was a combination of employment status and problems encountered in the working situation, including job loss of any cause and/or imminent job loss, defined as a failure to achieve an ACR20% response and either a WIS score deterioration or a persistently high WIS score ( $>17$ ). Job loss attributable to RA, working days lost and the WIS score were among the secondary outcome parameters.

Although all-cause job loss and/or imminent job loss during the 56-week study was significantly lower with adalimumab plus MTX (14 of 75 patients) compared with MTX alone (29 of 73 patients;  $p = 0.005$ ), at the primary end point of 16 weeks, the difference did not reach statistical significance (12 of 75 vs 20 of 73 patients;  $p = 0.092$ ). According to the authors, the lack of effect at 16 weeks was likely owing to early drop out in the MTX group. Job loss attributable to RA occurred in two patients in the MTX plus adalimumab group and four patients in the MTX plus placebo group ( $p = 0.386$ ).

Concerning working days lost, at week 56 the amount of working time lost was significantly less in the MTX plus adalimumab group (8.6%) compared with the MTX plus placebo group (18.4%;  $p = 0.038$ ).

With respect to problems encountered in the working situation, the improvement of the WIS score was significantly greater in the MTX plus adalimumab group ( $-8.1$ ) than in the MTX plus placebo group ( $-5.4$ ;  $p = 0.025$ ).

Data from an open-label extension study of 486 RA patients receiving adalimumab monotherapy who previously failed at least one DMARD and had baseline work status information were compared with data from 747 RA patients receiving DMARD therapy in a Norway-based longitudinal registry [31]. The primary outcomes in this study were the time patients remained at work and the likelihood of stopping work.

During a 24-month period, the 158 adalimumab-treated patients who were working at baseline worked 7.32 months longer (95% CI: 4.8–9.1) than did the 180 DMARD-treated patients, controlling for differences in baseline characteristics. Regardless of baseline work status, patients receiving adalimumab worked 2.0 months longer (95% CI: 1.3–2.6) and were significantly less likely to stop working than those receiving DMARDs (hazard ratio 0.36 [95% CI: 0.30–0.42] for all patients and 0.36 [95% CI: 0.15–0.85] for patients working at baseline, respectively).

van den Hout *et al.* recently published the results of a cost-utility analysis of treatment strategies in 508 patients with recent-onset RA [32]. This randomized study compared four adaptive treatment strategies, to investigate whether combinations of DMARDs, corticosteroids or TNF antagonists should be the initial treatment in RA, or should be reserved for patients failing monotherapy. For the purpose of a detailed cost analysis, the contract hours of paid work and absenteeism were recorded over a period of 2 years. In this study, it was found that worked hours were significantly different and highest for patients with initial combination therapy with infliximab.

Hoving *et al.* published a prospective, single-arm intervention study in 59 patients with established RA of working age [33]. All patients received fortnightly subcutaneous injections of 40 mg adalimumab. Perceived work ability was the only work-related outcome measure in this study. It was determined by means of the Work Ability Index, which asks patients to rate their current work ability using the lifetime best work ability as the reference.

It was found that in the subgroup of 26 patients with paid work, at 6 months perceived work ability increased significantly. In

addition, the decrease in costs associated with production loss of paid work was statistically significant (mean total costs per week of €40.4 [SD: 101.3] at baseline and €21.7 [SD: 85.8] at 6 months).

### Health economic issues regarding anti-TNF & productivity

The three studies that reported on anti-TNF and productivity costs in RA [26,32,33] all used the human-capital method to value productivity. This method calculates productivity costs by first estimating the patients' lost hours of production, and then multiplying those hours by the patients' gross hourly wage. In the study by Laas *et al.*, the use of anti-TNF agents did not lead to an improvement in productivity costs [26]. The study by Hoving *et al.* did show an improvement in productivity, but the associated savings in productivity were small compared with the increase in medication costs [33]. In both these studies the disease duration was relatively long. In contrast, patients in the study by van den Hout *et al.* had early-onset RA [32]. In this study the savings on paid and unpaid productivity together largely compensated for the high costs of anti-TNF agents: compared with the next best alternative (initial combination therapy with corticosteroids) medication costs were €16,949 higher, but productivity cost were €14,428 lower. However, this study also showed that the way productivity was valued had a considerable effect on estimated costs. Besides the human-capital method, van den Hout *et al.* applied the friction-cost method, which takes the employer's perspective and only counts costs until the absent patient is replaced by another employee. According to this friction-cost method, the productivity costs did not differ among the treatment groups.

Apart from primary data, the impact of anti-TNF agents on productivity costs may also be examined using mathematical models. Using such models, estimates of productivity costs can be obtained from clinical studies, without actually measuring productivity. However, so far the validity of these models has been questionable. Some have estimated productivity costs as one-time or three-times the medical costs [34]. This type of model is based on the observation from many cost-of-illness studies that productivity costs in RA outweigh the medical costs. However, it is unlikely that the ratio between productivity costs and medical costs is transferable across different RA populations or over time. Others have modeled the relationship

between productivity and the Health Assessment Questionnaire (HAQ) score (disability as measured by the HAQ) [35–38] or the relationship between retirement rate and the HAQ score [39]. These models may be more transferable than those based solely on medical costs, but they still disregard that relationships may change with the disease duration. Therefore, mathematical models for productivity need to be further developed and validated before they can be used as valid alternatives for primary data.

### Discussion

The number of studies on the effect of anti-TNF agents on work disability is limited, and the available studies vary with respect to their methodological quality.

Two studies had an observational design, making it difficult to draw any conclusion on a possible causal relationship between anti-TNF treatment and work disability [26,33]. Both studies included relatively few RA patients who were gainfully employed or of working age at baseline. Moreover, in the study by Laas *et al.*, the data on work disability in RA patients were not presented separately from those of patients with other forms of chronic arthritis [26].

In four studies, cohorts of patients using either anti-TNF agents or not were compared [24,27,28,31], three with a positive and one with a negative conclusion. Overall, the interpretation of the results of these studies is hampered by the nonrandomized design, with ensuing possible differences in the timing of inclusion in the study and the characteristics of the patient groups [22]. It is generally thought that these effects and differences cannot be simply disentangled by statistical techniques [22]. Moreover, in these studies little information is given on the timing of work disability. In one of the four comparative studies [28], the analyses were limited to patients who were still employed at baseline. Therefore, from this study it remains unclear whether treatment with anti-TNF agents may allow patients who were previously work-disabled to return to work after initiation of therapy [22]. The problem of potential differences between disease activity and disease characteristics of patients from different cohorts may also be present in matched case-control designs, as employed in the study by Allaire *et al.* [29].

In the three available randomized controlled trials, all including patients with early RA (a disease duration of less than 2 years [30,32] or less than 3 years [25]), in general a positive effect of anti-TNF agents as compared with conventional

DMARD therapy (either sequential monotherapy or combinations of DMARDs and/or prednisolone) on work disability was seen.

Evaluating the available studies, the current literature seems to suggest that anti-TNF agents can indeed protect against RA-associated work disability, with the strongest evidence concerning studies in patients with early RA. Due to methodological weaknesses of studies among patients with longer disease duration, their results should be interpreted with care. However, it could be hypothesized that in patients with established RA, the impact of anti-TNF on work disability is indeed smaller than in patients with early RA. Workplace burden is thought to begin early in the disease course, in some cases even before diagnosis, with reduced productivity and increased absenteeism due to pain, fatigue and visits to healthcare providers [40]. As RA progresses, employees may find that they are not able to continue working in their job, and switch jobs or occupations, or may leave the workforce for part of their working hours or altogether, usually with partial or full work disability pension [40].

This progression of workplace impact would imply that in patients with a longer disease duration, job loss is already substantial, and for those who have been able to maintain their job, productivity may be less affected by their RA than in patients with early disease, because they are a selected group of patients. The hypothesis of a potentially more favorable effect of anti-TNF agents on work disability in early RA compared with established disease is supported by observations with conventional DMARDs, demonstrating that in patients with recent-onset RA, prompt induction of remission translates into maintenance of work capacity [41]. Similar to the results of the study by Smolen *et al.* [25], this study found that the impact on work disability was mainly determined by achieving remission rather than by the treatment regimen. These findings suggest that, more than a specific therapeutic strategy, reduction of disease activity should be the leading principle to reduce the workplace burden in RA patients.

The available data suggest that in the future more randomized controlled clinical trials are needed, with sufficient numbers of patients with early RA. It should be noted in this respect that the workplace burden is likely to begin even before diagnosis, so that studies need to include patients directly after a diagnosis is made. In addition, follow-up needs to be long-term. There are several potential beneficial or adverse effects of anti-TNF therapy that may

have an impact on work disability, but can only be seen after a considerable period of follow-up, including, for example, its impact on joint replacement and other surgery rates, effects on the development of malignancies, infections and cardiovascular events.

A striking observation of the present overview was the large variety of outcome measures used to measure work disability. A direct comparison among studies is hampered by the variety of definitions and measurement methods used to determine work cessation, absenteeism, problems encountered and reduced productivity while still working. In general, the focus is on work cessation and absenteeism, although loss of productivity while working may be burdensome for both patients and employers [40]. The appropriate measurement of loss of work productivity while working may also help to detect changes in work disability over time where follow-up is relatively short and the incidence of job loss or absenteeism is low.

The development and usage of a core set of outcome measures representing all types of work disability is strongly needed. This core set needs to be suitable for economic evaluations as well. Concerning economic analyses, several countries have guidelines for the methodology that should be used in economic evaluations of healthcare interventions like anti-TNF agents. These guidelines differ on whether productivity costs should be included in the analysis and, if so, whether they should be valued according to the friction-cost method or the human-capital method [42].

It is important to realize that this can have a considerable impact on whether the high costs of anti-TNF agents are considered economically acceptable and for which patients. So far, economic studies suggest that, in patients with long disease duration, the gain in effectiveness and the savings on productivity are insufficient to justify the current high costs of anti-TNF agents. In patients with early-onset RA, productivity costs may compensate sufficiently for the high medication costs, but only if productivity costs are given full weight using the human-capital method. Further investigations are needed to assess the long-term effect of anti-TNF agents on productivity costs. In addition, the impact on the value of unpaid work and reduced productivity while working is largely unknown, warranting additional studies [43,44].

In addition, the literature lacks discussion of successful nonpharmacological interventions or comprehensive rehabilitation programs that

keeps employees in the workforce [40,45]. To target these interventions at those employees with imminent work disability, increased awareness of work disability among rheumatologists, clinical nurse specialists and other health professionals involved is needed. Moreover, simple screening tools that are feasible in daily practice need to be used systematically, for example in connection with the initial and follow-up assessments of early arthritis clinics.

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### Executive summary

#### Rheumatoid arthritis & work disability

- The prevalence of work disability, including work cessation, sick leave and decreased productivity while being at work, among patients with rheumatoid arthritis (RA) is substantial.
- In recent studies, a trend towards a decline in work disability in RA is seen, which is considered to reflect improvements in drug treatment over the past decades.

#### Anti-TNF agents & work disability

- The number of studies evaluating the impact of anti-TNF agents on work disability in patients with RA is limited.
- In the few available randomized controlled trials, in general a positive effect of anti-TNF agents on work disability in early RA is observed. In established RA, the evidence is scarce.

#### Health economic issues

- The way productivity is valued has a considerable impact on the outcomes of health economic analyses of anti-TNF agents in RA.
- Depending on the way productivity is valued, savings on productivity may compensate for the high costs of anti-TNF agents in early RA.

#### Future perspective

- Future studies on the impact of anti-TNF agents on work disability in RA should not only take into account work cessation, but also sick leave, reduced productivity levels while at work and unpaid work.
- Mathematical models for productivity need to be further developed.
- Future studies should have a substantial duration of follow-up, as the annual incidence of work disability is relatively low, and a substantial proportion of patients who stop working may return to work later.

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