Sick leave in patients with ankylosing spondylitis before and after anti-TNF therapy: a population-based cohort study

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Abstract

Objective. To study levels of sick leave and disability pension before and after TNF-antagonist therapy in AS patients.

Methods. Using the population-based South Swedish Arthritis Treatment Group register, we identified 139 AS patients (aged 18–58 years, 78% men), who between January 2002 and December 2008 started their first treatment with adalimumab, etanercept or infliximab. We linked data to the payment register by the Swedish Social Insurance Agency and calculated the proportion on sick leave in 30-day intervals from 12 months before treatment start until 12 months after. For each AS patient, we randomly selected four subjects from the general population matched for age, sex and area of residence.

Results. One to 3 months before treatment, an average of 24% of AS patients were on sick leave. During the first 6 months after treatment start, this fraction dropped to 15%, and further declined to 12% at 12 months (P < 0.001). Comparing AS patients with the general population, the relative risk of being on sick leave 3 months before treatment, treatment start and 12 months after treatment start was 8.0 (95% CI 4.6, 13.9), 9.2 (95% CI 5.4, 15.7) and 4.0 (95% CI 2.1, 6.3), respectively. The decrease in sick leave was not substantially offset by changes in disability pension.

Conclusion. There is a decline in sick leave during the first 12 months after initiation of TNF-antagonist treatment in AS patients not explained by societal factors or secular trends. The proportion of AS patients on disability pension remained unchanged during the observation period.

Key words: work disability, sick leave, ankylosing spondylitis, spondyloarthritis, anti-TNF-α therapy, biologics register, infliximab, etanercept, adalimumab.

Introduction

The chronic inflammatory disease AS affects both axial and peripheral joints. Prevalence of AS is higher in men than in women with a ratio of ~2–3: 1 [1]. A minority of patients experience severe extra-articular events such as uveitis and cardiac complications [2, 3]. The disease often causes substantial impairment of the patient, both in function and health-related quality of life. Reduced work ability leading to sick leave is a common consequence of AS [4, 5] and may contribute to psychosocial and economic (direct and indirect) negative consequences for the individual as well as for society [6, 7].

Following the introduction of TNF inhibitors, several aspects of the disease, including disease activity, spinal mobility, peripheral arthritis and enthesitis have improved dramatically [8–14]. However, considering the high costs and possible risks of anti-TNF therapy, these treatments have recently received greater attention regarding health economic calculations. The proportion of work-disabled patients with AS is reported to vary between 9 and 36%, and anti-TNF has been shown to affect this proportion [15, 16]. Therefore, even moderate changes to
work-disabled patients would have dramatic economical impacts of indirect costs of AS, which in turn is important when evaluating the true costs of anti-TNF treatments.

The aim of the present study was to assess the extent of sick leave and disability pension in AS patients before and after the start of either adalimumab, etanercept or infliximab therapy (referred to as anti-TNF treatment). We used patient data from a regional anti-TNF treatment register [17] and retrieved information of sick leave and disability pension from an independent source, the Swedish Social Insurance Agency (SSIA) via the MORSE project, www.morse.nu. Further, we compared our results with subjects randomly drawn from the general population matched for age, sex, residential area of the AS patients and time of anti-TNF initiation.

Methods

The patient cohort was identified as patients with active AS, starting anti-TNF therapy for the first time between January 2002 and December 2008. They were prospectively monitored as part of the South Swedish Arthritis Treatment Group (SSATG) register cohort, as previously described [17]. The coverage of the register has been reported to >90% of all treatments for RA patients started on biologics [17]. Patients eligible for inclusion had a clinical diagnosis of AS requiring first course of anti-TNF treatment. We validated the accuracy of the AS diagnoses in SSATG by the use of an independent cohort of AS patients at one of the treatment centres in southern Sweden with valid diagnoses, as described in a previous publication [18], and subsequently linked to the SSATG register. The validation revealed that 90% (26 out of 29 patients) of the anti-TNF-treated patients fulfilled the modified New York criteria for AS [19].

Anti-TNF therapy in AS patients included in the SSATG register was initiated due to high disease activity according to the clinical use of national guidelines, but no predefined level of disease activity was required. Instead, decisions to initiate therapy with a certain agent were left to treating physicians. Glucocorticoids could be administered systemically or by local injections before or during the study period, and concomitant use of NSAIDs or non-biologic DMARDs was allowed. As we only wanted to include subjects with full work availability potential during the observation period, we excluded patients aged <17 years and >59 years. Also, only patients living within the Skåne County in southern Sweden were included, excluding a total of 104 patients of the original cohort (Fig. 1). The patients were subsequently cross-linked to data from the SSIA and we calculated the proportion of patients with ongoing sick leave or disability pension in 30-day intervals from 12 months before treatment start until 12 months after [18].

At the start of anti-TNF therapy, baseline characteristics were reported by the treating physicians using a standardized protocol. This included information on demographics, disease duration, symptoms, data on past and present anti-rheumatic therapy, results of laboratory examinations and clinical variables allowing the calculation of disease activity according to the BASDAI [20]. Functional status was assessed by the BASFI [21], and by the validated Swedish version of the HAQ [22]. Furthermore, results of self-scored visual analogue scales for pain (VAS pain) and general health (VAS global) were also reported, along with evaluators’ global assessment of disease activity on a five-grade Likert scale (Eval. global).

Etanercept was administered twice weekly with a 25-mg s.c. dose initially, later 50 mg once weekly was often used. Infliximab was infused at 3 mg/kg at 0, 2, 6 and then every 8 weeks. Depending on efficacy, the dose of infliximab could then be increased in steps of 100 mg to a maximum of 500 mg administered at 4–8-week intervals. The average dosage after 6 months was ~4.5 mg/kg every 8 weeks. Adalimumab was administered as a 40-mg s.c. dose every other week.

Using the Swedish population register, which includes information on date of birth, sex and residential address of all Swedish residents, we randomly selected four subjects for each AS patient matched for age, sex, area of residence and time period of study. This cohort represents the background population in this study.

The Swedish social insurance, which provides financial protection for individuals at working age in connection with illness or injury, covers everyone that legally lives or works in Sweden. We defined sick leave as days with sick pay or sickness benefit of any degree paid by the SSIA (all sick leave >15 days is continuously and prospectively registered). Sick pay for shorter periods of inability to work (≤14 days) is paid by the employer, and therefore not included in this study. Disability pension is defined as a permanent social benefit paid by the SSIA. For the purpose of this study, we included all kinds of work disability for both the AS patients and the background population irrespective of the cause, i.e. for the AS patients, the sick leave could be directly or indirectly related to AS or it could not be so.
It should be noted that in Sweden persons can work part time (25, 50 or 75%) and receive sick pay or disability pension for the remaining part of a full-time working schedule, which in Sweden is 5 days (40 h) per week. Therefore, we also calculated the net amount of time the AS patients and the matched background population were work disabled during the observed period, i.e. 10 days with 50% part-time sick leave equal 5 net days. Over a 4-week work period (20 work days) that would equal to 25% net time on sick leave. This fraction serves as a more accurate estimate for indirect costs of the disease burden in health economics.

Cross-linking data from the SSIA with health-care data were approved by the local ethical committee in Lund (No. 514/2007). The quality control character of the SSATG register makes it part of the legislative documentation demanded in Sweden, and no formal ethical approval was required for using the register for this study purpose. This has been formally tested twice by the ethical committee.

Statistics

We present baseline characteristics of patients starting anti-TNF treatment as mean (s.d.), unless otherwise stated. McNemar’s test was used to compare the average proportion of AS patients on sick leave 1–3 months before anti-TNF treatment start with 10–12 months after using the intention-to-treat principle. We also calculate the relative risk to be on sick leave compared with the background population including the 95% CI. To look for potential confounding factors, we stratified the outcome data according to sex and type of anti-TNF treatment as well as median age, disease duration, BASFI and BASDAI. Finally, we analyse sick leave trends during the study period using univariable co-variance analysis. Wilcoxon’s paired rank test was used for studying changes in BASDAI, BASFI, VAS pain and VAS global during the 12-month period of anti-TNF treatment. Two-tailed P < 0.05 was considered statistically significant.

Results

During the study period, 139 biologically naive patients aged 18–58 years with active AS initiated their first anti-TNF inhibitor treatment. The flow of patient selection and exclusion is shown in Fig. 1. Men constituted 78% of the cohort and mean (s.d.) disease duration of 14 (11) years (Table 1). One year after treatment start, 111 patients remained on the initial therapy, 24 had changed to a second anti-TNF therapy and 4 patients had stopped anti-TNF therapy (Fig. 1). There were no differences in age, sex, disease duration, CRP level, ESR, VAS global, Eval. global, previous DMARDs and type of anti-TNF treatment for patients with complete baseline data compared with patients with incomplete data. However, patients missing BASDAI and BASFI scores had higher mean (s.d.) VAS global values [63 (21)] than patients with complete data [56 (24)] (P = 0.008).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 139</th>
<th>Missing data (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>41 (10)</td>
<td></td>
</tr>
<tr>
<td>Gender: men, n (%)</td>
<td>109 (78)</td>
<td></td>
</tr>
<tr>
<td>Disease duration, mean (s.d.), years</td>
<td>14 (11)</td>
<td></td>
</tr>
<tr>
<td>VAS pain (0–100 mm), mean (s.d.)</td>
<td>60 (22)</td>
<td>10</td>
</tr>
<tr>
<td>VAS global (0–100 mm), mean (s.d.)</td>
<td>58 (23)</td>
<td>10</td>
</tr>
<tr>
<td>Doctor’s evaluators’ global assessment (0–4 mm Likert scale), mean (s.d.)</td>
<td>2.0 (0.8)</td>
<td>6</td>
</tr>
<tr>
<td>ESR, mean (s.d.), mm/h</td>
<td>30 (25)</td>
<td>7</td>
</tr>
<tr>
<td>CRP, mean (s.d.), mg/l</td>
<td>25 (28)</td>
<td>7</td>
</tr>
<tr>
<td>BASDAI score (0–10), mean (s.d.)</td>
<td>5.1 (2.0)</td>
<td>71</td>
</tr>
<tr>
<td>BASFI score (0–10), mean (s.d.)</td>
<td>4.1 (2.1)</td>
<td>73</td>
</tr>
<tr>
<td>HAQ score (0–3), mean (s.d.)</td>
<td>0.75 (0.56)</td>
<td>11</td>
</tr>
<tr>
<td>Previous number of DMARDs, mean (s.d.)</td>
<td>1.1 (0.9)</td>
<td></td>
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<tr>
<td>Type of anti-TNF therapy, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Infliximab use</td>
<td>63 (45)</td>
<td></td>
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<tr>
<td>Etanercept use</td>
<td>57 (41)</td>
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<tr>
<td>Adalimumab use</td>
<td>19 (14)</td>
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</table>

Patient-related clinical outcome decreased significantly during the first year of anti-TNF treatment. Thus, mean (s.d.) VAS pain and VAS global decreased from 60 (22) and 58 (23) at baseline to 35 (19) and 33 (18) after 12 months, respectively (n = 129, P < 0.001). Likewise, BASDAI and BASFI levels decreased significantly; however, the results are not shown due to insufficient data recordings.

Work disability analysis

Figure 2A shows 30-day period prevalence of sick leave for AS patients and the background population during the 1-year period before and after initiation of anti-TNF treatment. At 1–3 months before treatment start, 24% (mean) of the AS patients were registered for sick leave, and at treatment start that proportion was 28%. After the first 6 months, this fraction had dropped to 15%, and the level further declined to 12% at the end of the study period. The change from 1–3 months before treatment to 10–12 months after (mean 14%) was statistically significant (P < 0.001). Comparing AS patients with the background population, the relative risk of being on sick leave was 8.0 (95% CI 4.8, 13.9) 3 months before treatment start, 9.2 (95% CI 5.4, 15.7) at treatment start and 4.0 (95% CI 2.1, 6.3) at 12 months.

When analysing the AS patients for changes in sick leave over time using covariance analysis, the proportion of AS patients on sick leave showed a significant change after initiation of anti-TNF therapy (P < 0.001). On the other hand, no such corresponding change was found for disability pension.

As presented in Fig. 2B, the proportion of AS patients on disability pension changed slightly during the study
period; however, the proportion on disability pension at 12 months before anti-TNF treatment start and 12 months after did not differ with statistical certainty (19 vs. 26%, P = 0.887, data not shown). The relative risk of disability pension for AS patients compared with the background population was 4.4 (95% CI 2.8, 6.7) at treatment initiation and increased to 5.1 (95% CI 3.3, 8.1) after 1 year of anti-TNF treatment.

When assessing the change in overall proportion of AS patients determined to be medically unfit to work, either temporarily (sick leave) or more permanently (disability pension), the decrease after anti-TNF treatment initiation (Fig. 2A) is somewhat compensated by the change in proportion of patients with disability pension (Fig. 2B). Still, the trend of increased work disability in AS patients before anti-TNF treatment is clearly broken (or even somewhat reversed) after initiation of therapy (P < 0.001).

Table 2 presents net amount of work disability to compensate for part-time sick leave that is an option in the Swedish social security system. Thus, the anti-TNF-treated patients are on sick leave 18% of the time at treatment initiation, which declines to 10% after 1 year of treatment (P < 0.001). Although steadily increasing, the absolute amount of disability pension remained relatively similar over the study period, from 20.6% at the start of anti-TNF to 21.7% after 1 year of treatment (P = 0.923). The corresponding numbers for the background population is 3- to 6-fold lower and remained unchanged over the study period.

Subgroup analysis
After stratification for sex and type of anti-TNF treatment, we did not find any significant effect of these characteristics with regard to changes in either sick leave or disability pension (data not shown).

The decrease in sick leave in AS patients with disease duration of <14 years (the mean disease duration in the study cohort) changed from 34 to 16% compared with a decline from 22 to 10% for patients with >14 years of disease duration (P = 0.337). Patients with an age of >40 years showed a decline in sick leave from 33 to 12% compared with younger patients who had a decline from 23 to 13% during the first year of anti-TNF treatment (P = 0.097). On the other hand, disease duration and age both showed higher levels of disability pension in the older patients with longer disease duration. Thus, in patients with disease duration of >14 years, 32% had disability pension at treatment initiation, which remained unchanged at 33% 12 months after anti-TNF treatment (P = 0.652). Patients with a shorter disease duration showed a significant increase in disability pension from 13 to 20% during the first year of anti-TNF therapy (P = 0.004). Likewise, in patients aged >40 years, 35% of the patients had disability pension at treatment initiation, which increased to 38% 12 months after treatment (P = 0.522). The corresponding lower levels for younger patients were 9% with an increase to 14% (P = 0.228).

We also performed secondary analyses with stratification based on the patients with data available for BASDAI and BASFI, but no significant differences were found (data not shown). It should be noted that baseline data for BASDAI and BASFI were incomplete (Table 1), hampering this analysis.

Discussion
This population-based cohort study provides evidence of a rapid and sustained decrease in sick leave among AS patients after start of anti-TNF therapy. The changes in
The patients in an irreversible stage of work disability.

Longer disease duration and higher age seems to position preferably be used in an earlier phase of the disease, as and higher age, could indicate that anti-TNF agents should this finding, in combination with the increased level of dis-

tance on permanent disability pension, which showed a impact on permanent disability pension, which showed a.

Between countries should be interpreted with care. It is also have a window of opportunity in the earlier stages, but this is currently been debated.

Periods of sickness of employees ≤15 days are not registered by the SSIA and hence not included. However, it is reasonable to assume that short periods of sick leave in most cases could be attributable to intermittent infections or injuries, thus being somewhat more evenly distributed between AS patients and the general population.

It should be noted that no valid data were available on the actual amount of working hours per week in the patient group or in the background population. However, in the Scandinavian social security system you receive work disability reimbursement for the actual time you are not able to work. Furthermore, we do not have any data on the working performance of the subjects registered as being at work. This may be a source of bias when performing health economic calculation extrapolated from the data presented in the current study.

The open, observational setting of this study naturally has limitations in its methodology such as possible bias regarding patients selected for treatment, assignment of treatment and collection of clinical data. However, our study outcome, the work disability data, was collected from an independent and blinded source for both the AS patients and the general population hosted by the SSIA, and is of high quality as it is linked to the actual payment system. Higher levels of missing data regarding certain baseline parameters (Table 1) were another result of the observational setting. On the other hand, observational studies remain crucial in offering actual treatment and outcome information from daily clinical practice, which is not obtained in the randomized control trial setting.

Further, it is likely that the initiation of anti-TNF treatment occurred at a very active stage of the patient’s disease; hence regression to the mean phenomenon is expected, also so for sick leave. Having no reference cohort with similar disease severity but with conventional treatment only, limits our possibilities to evaluate the effect of this phenomenon. However, it should be noted that the phenomenon of regression towards the mean cannot extend a period longer than the mean duration of a flare. Thus, the

<table>
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<tr>
<th>Table 2 Net amount of sick leave and disability pension during first year of anti-TNF treatment expressed as per cent of full working time</th>
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<tr>
<td><strong>Work disability</strong></td>
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<tr>
<td>Sick leave</td>
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<td>AS patients</td>
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<tr>
<td>Background population</td>
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<tr>
<td>Disability pension</td>
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<tr>
<td>AS patients</td>
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<td>Background population</td>
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P-values represent significant differences within strata during follow-up period (n = 139).

Sick leave status were also associated with significant improvements in the clinical parameters VAS pain and VAS global. This is an important finding as we have previously shown that patients with AS suffer from substantial impairment in work ability [18]. The fraction of permanent disability pension increased slightly with no significant impact of anti-TNF therapy. Also, the comparison with the background population shows a 9-fold increased risk of being on sick leave in AS patients at anti-TNF treatment start. This relative risk declined to 4-fold after 1 year of anti-TNF treatment. Our findings are in agreement with, but in the higher spectrum of, what has been reported earlier [5, 6, 16, 18, 23]. Boonen et al. [6] described that the risk for withdrawal from work in The Netherlands was about three times higher in patients with AS, and that work disability in three European countries was higher than expected in the general population [6]. In a recently published AS cohort from southern Sweden, the relative risk for being work disabled compared with matched controls was 1.8 [18]. However, it should be noted that patients receiving anti-TNF represent a selection of the most severe cases of AS, as seen in Table 1, and a higher level of work disability is therefore to be expected in this group when compared with AS patients in general. In agreement with another anti-TNF-treated cohort presented by Listing et al. [15], the fraction of patients being on any sick leave after longer period of anti-TNF treatment showed a significant decline to lower and rather similar level as our cohort, 14 and 12%, respectively. However, due to the small sample size in the study of Listing et al. [15], heterogeneity of populations studied, differences in methodology used, as well as diverse social security systems, comparisons between countries should be interpreted with care.

In contrast, anti-TNF therapy did not have any significant impact on permanent disability pension, which showed a slight and insignificant change during the observation period. This finding, in combination with the increased level of disability pension in patients with longer disease duration and higher age, could indicate that anti-TNF agents should preferably be used in an earlier phase of the disease, as longer disease duration and higher age seems to position the patients in an irreversible stage of work disability.

It has been argued that other aspects of the disease also have a window of opportunity in the earlier stages, but this is currently been debated [24].
continuous decline in sick leave seen throughout the 12-month period can hardly be attributed to this phenomenon alone. Also, the significant and nearly 50% decline in pooled 3-month data before anti-TNF treatment compared with pooled data at the end of the 2-year study period contradicts that the changes in sick leave observed in this study is solely contributed to regression towards the mean.

In conclusion, we provide evidence that anti-TNF therapy is associated with a significant and sustained decline in sick leave during the first 12 months of treatment. In contrast, disability pension remained at a rather high level with no substantial impact of anti-TNF treatment during the first year.

**Rheumatology key messages**
- There was a marked decline in sick leave during anti-TNF treatment in AS patients.
- There were significant improvements in VAS pain and VAS global scores during anti-TNF treatment in AS patients.

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