Smoking did not modify the effects of anti-TNF treatment on health-related quality of life among Australian ankylosing spondylitis patients

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Abstract

Objective. The aim of this study was to examine the impact of smoking on health-related quality of life (HRQoL) among AS patients who were taking biologic DMARDS.

Methods. This is a longitudinal cohort study of AS patients with anti-TNF treatment in the Australian Rheumatology Association Database (2003-11). They were assessed using the 36-item Short Form Health Survey (SF-36), Assessment of Quality of Life (AQoL) and HAQ for spondylitis (HAQ-S) on a biannual basis. Linear mixed models were used to assess the impact of smoking on HRQoL outcomes over the first 2 years of treatment.

Results. Four hundred and twenty-two patients [73% male, mean age 44.9 years (s.d. 12.7) provided 1189 assessments for the study. Current smokers (n = 79) were slightly younger, more likely to be male, less likely to use or to have previously used prednisolone and had a slightly shorter disease duration than past smokers (n = 138) or non-smokers (n = 205). After adjusting for smoking, gender, age, education, employment, co-morbidities and medication use, including DMARDS, anti-inflammatoryatories and analgesics, all the HRQoL measures improved significantly over the study period and the improvements were not modified by smoking status (all P-values >0.36). Current smokers tended to have poorer HRQoL on the SF-36 physical score [-1.93 (95% CI -3.94, 0.09), P = 0.06] and the HAQ-S score [0.10 (95% CI 0.01, 0.20), P = 0.07] compared with non-smokers.

Conclusion. Among AS patients, active smoking did not diminish or modify the improvements in HRQoL from anti-TNF treatment, even though current smokers compared with non-smokers tended to have poorer scores in some HRQoL measures.

Key words: ankylosing spondylitis, anti-TNF drugs, quality of life, SF-36, smoking.

Introduction

Many studies have linked smoking to poor health-related quality of life (HRQoL) [1-3]. In a general population survey in Finland during 2000-01, current regular smokers scored significantly worse in dimensions of mobility, usual activities, breathing, depression, distress and vitality than did non-smokers [1]. In another study of 17 800 US men and women in 2006, McClave et al. [2] reported that current smokers compared with non-smokers had higher scores in measures of life dissatisfaction, anxiety symptoms, depressive symptoms and sleep impairment. This relationship is also observed among RA patients who already have poor HRQoL [4]. Importantly, smoking cessation is
associated with increased HRQoL scores in a randomized controlled trial of 1504 participants [5].

Environmental factors have long been investigated as possible triggers and risk factors for the onset and progression of rheumatic diseases. Recent interest has focused on smoking after studies found that smoking is both a risk factor for RA development and is associated with higher disease activity [6, 7]. Moreover, smoking has also been found to diminish response to both non-biologic and biologic DMARDs in the treatment of RA [8–10]. Interestingly, smoking does not appear to significantly worsen the radiographic progression of RA [11]. As a modifiable risk factor, smoking cessation has become a major target in the treatment of RA and, in light of these findings, interest has been directed towards other rheumatic diseases to see whether smoking has similar risk effects in these conditions.

AS is the prototypic seronegative SpA, characterized by inflammatory back pain, sacroiliitis and progressive syndesmophyte formation as well as peripheral arthritis and extra-articular manifestations [12]. AS is more common in males than females and shows a genetic predisposition with the presence of HLA-B27. Previous studies in an Australian cohort of AS patients found that current smoking was associated with more severe disease activity and impaired function compared with non-smokers or past smokers based on the BASDAI and BASFI, respectively [13].

The aim of this study was to examine the impact of smoking on HRQoL among Australian AS patients who were taking biologic DMARDs. Specifically we wanted to determine (i) whether there are differences in HRQoL measures between current smokers, past smokers and non-smokers among AS patients and (ii) if smoking status modifies the responses to treatment with biologic DMARDs over the first 2 years of the treatment.

Methods

This is a longitudinal cohort study using data from an inflammatory arthritis patient registry.

Data source

The Australian Rheumatology Association Database (ARAD), established in 2001, is a voluntary national Australian registry of inflammatory arthritis patients. The registry is designed to collect longitudinal health information on patients with inflammatory arthritis, particularly with respect to the use of different therapeutic agents including non-biologic and biologic DMARDs [14]. Patients with AS were first enrolled in 2003. They could enter the database any time after giving their consent and might provide the first assessment before, at the beginning of, during or even after their first biologic DMARD treatment. After enrolment through their rheumatologist or by self-referral, patients are followed on a biannual basis with a standardized questionnaire. The data collected in ARAD include demographic information; smoking status; education level; employment; year of disease onset and diagnosis; presence of co-morbidities such as cardiovascular disease, lung disease, depression, mental illness, diabetes, kidney disease, liver disease, gastrointestinal disease, anaemia or other blood disease, eye disease, neurological disease, osteoporosis, tuberculosis or thyroid disease (i.e. lung or cardiovascular diseases, other co-morbidities and non-co-morbidities); medication use (biologic DMARDs, non-biologic DMARDs, NSAIDs, glucocorticoids); pain and global arthritis condition in the last week and HRQoL measures. Ethics approval for ARAD was granted by 20 committees and organizations across Australia. Only de-identified data were made available to researchers who carried out the data analysis.

Study subjects

Study subjects were AS patients in ARAD from March 2003 to September 2011. The diagnosis of AS was made by the treating specialist rheumatologist. However, modified New York criteria were not mandatory for the diagnosis in Australia. For access to biologic DMARD therapy in Australia, confirmation of radiological changes of sacroiliitis is a mandatory requirement. The primary endpoint of this study is to assess possible interaction between smoking status and the effect of biologic DMARD treatment. That is, we wanted to examine whether the slope (rate of change) over 2 years for the effect of the treatment is the same among all AS patients regardless of smoking status. Therefore the study was limited to subjects who were on their first anti-TNF treatment (i.e. etanercept, adalimumab, infliximab, golimumab) and had at least one assessment (questionnaire) within 27 months of treatment initiation (see Table 1 for the number of assessments at each time point). The baseline characteristics of the AS cohort have been described elsewhere [15].

Patient reported HRQoL and physical function outcomes

The 36-item Short Form Health Survey (SF-36) is a generic health status indicator [16, 17] that has been shown to correlate with AS-specific measures such as the AS-specific quality of life measure (ASQoL) [18]. SF-36 measurements can be summarized into a physical component summary (PCS) and a mental component summary (MCS) score ranging from 0 to 100, with higher scores representing better health and functioning. The Assessment of Quality of Life (AQoL) is a multi-attribute utility instrument measuring HRQoL in five dimensions recommended by the World Health Organization, including illness, independent living, social relationships, physical senses and psychological well-being [19]. The original items were derived through focus groups of doctors and researchers and were then validated with a construction sample of hospital patients and community members chosen at random. Utilities were derived through iterative time trade-off exercises from a healthy population’s perspective. The scale scores are converted into an overall index where negative values indicate a state worse than death, 0 represents death and 1 represents perfect health. The HAQ for spondylitis (HAQ-S) is a physical function
assessment instrument concerning eight areas of daily life—dressing, rising, eating, walking, hygiene, reach, grip and usual activities. Its score ranges from 0 to 3, with higher scores representing greater disability [20]. The BASDAI was collected on only a subgroup of the study subjects.

Data analysis
A time variable was created for analysis based on the timing of assessments. Assessments before initiation of the first anti-TNF were treated as prior-to-treatment assessment (giving a time value of −2.5), from initiation of treatment to <3 months as initial assessment (giving a time value of −1.5), from 3 to <9 months as the 6-month assessment (giving a time value of −0.5) and so on for every 6-month interval up to the 2-year assessment (assessment from 21 to <27 months, giving a time value of 2.5). This allows us to estimate within-individual changes in a HRQoL measure from anti-TNF therapy over the study period in a general linear mixed model and to test whether the slope of the change in the HRQoL measure is modified by smoking status (i.e. interaction between smoking status and time). The first data collection of each study subject was used for reporting the study subject’s characteristics. For description proposes, smoking status was defined via this baseline questionnaire as current smoker, past smoker or non-smoker. However, smoking status at the time of assessment was used in regression analysis and missing values (~5%) were imputed using the last value carried forward approach.

Differences in characteristics between current smokers, past smokers and non-smokers were compared using the chi-squared test or analysis of variance where appropriate. Linear mixed models were used to assess the impact of smoking status at the time of assessment on study outcomes over the study period, adjusting for potential confounders such as gender, education, employment and co-morbidity at the first assessment and age, use of non-biologic DMARDs, NSAID use and analgesic drug use at the time of assessment. In regression analysis, a study outcome might be modelled as a linear or quadratic function of time where appropriate. Models with both random intercept and random time coefficient and an unstructured covariance for the analyses were selected, as they fit the data better than random intercept models (data not shown). Interactions between smoking status and time were tested in all models and if no significant results (i.e. P > 0.05) were obtained, it was concluded that the effects of the biologic DMARD treatment were not dependent on or modified by smoking status. All analyses were performed using Stata version 11 (StataCorp, College Station, TX, USA).

Results
Baseline characteristics
There were 422 eligible study subjects [73% male, mean age 44.9 years (s.d. 12.7)] from 561 AS patients in the ARAD (2003–11). In total, the 422 subjects provided 1189 assessments from prior to initiation of the first biologic DMARD to 27 months after the initiation. At the time of biologic initiation, current smokers were slightly
younger, at 40.2 years (S.D. 9.8) compared with past smokers and non-smokers [48.5 years (S.D. 12.4) and 44.2 (S.D. 13.2), respectively, \(P < 0.001\)]. Disease duration was similarly slightly shorter in current smokers (\(P = 0.003\); Table 2). On the first (baseline) assessment, current smokers were also more often male, less likely to use or to have previously used prednisolone or salazopyrin and less likely to have a tertiary education than non-smokers.

At baseline, there were no differences with respect to co-morbidities, other medications including NSAIDs, pain in the last week or global arthritis condition in the last week between different smoking status (Table 2).

**Effects on HRQoL outcomes**

Based on all assessments and smoking status at the time of assessment, current smokers had a lower SF-36 physical score [current smoker 42.1 (S.D. 9.4), past smoker 42.7 (S.D. 10.2) and non-smoker 44.2 (S.D. 9.8); \(P = 0.008\)], a lower SF-36 mental score [current smoker 47.4 (S.D. 11.0), past smoker 49.1 (S.D. 9.5) and non-smoker 49.6 (S.D. 9.2); \(P = 0.03\)], a lower AQoL score [current smoker 0.62 (S.D. 0.23), past smoker 0.65 (S.D. 0.22) and non-smoker 0.67 (S.D. 0.22); \(P = 0.04\)] and a non-significant higher HAQ-S score [current smoker 0.66 (S.D. 0.56) and non-smoker 0.57 (S.D. 0.56); \(P = 0.10\)]. Table 1 presents these HRQoL outcomes by smoking status and assessment time. The results indicated that the study patients’ quality of life improved over a 2-year period regardless of smoking status and HRQoL measures. This is supported by positive coefficient values for the time variable in mixed regression models (Table 3). The changes in HRQoL measures over the study period

<table>
<thead>
<tr>
<th>TABLE 2 Characteristics of 422 first biologic users by smoking status a</th>
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<tbody>
<tr>
<td>Current smoker (n = 79)</td>
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<td>------------------------</td>
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<tr>
<td>At the beginning of the study</td>
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<tr>
<td>Female, n (%)</td>
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<td>Age, mean (s.d.), years</td>
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<td>Education (≤ high school), n (%)</td>
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<td>Employment (full time), n (%)</td>
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<td>BASDAI 4, mean (s.d.)</td>
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<td>Disease duration, mean (s.d.), years</td>
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<td>Pain (last week), mean (s.d.)</td>
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<td>Arthritis condition (last week), mean (s.d.)</td>
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<tr>
<td>Co-morbidity, n (%)</td>
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<tr>
<td>Lung/cardiovascular diseases</td>
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<td>Other co-morbidities</td>
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<td>Non-co-morbidity</td>
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<tr>
<td>Use of NSAID, n (%)</td>
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<tr>
<td>Use of analgesic drug, n (%)</td>
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<td>Use of prednisolone, n (%)</td>
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<td>Use of MTX, n (%)</td>
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<td>Current use</td>
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<td>Past use</td>
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<tr>
<td>Use of salazopyrin, n (%)</td>
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<td>Never taken</td>
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<tr>
<td>Current use</td>
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<td>Past use</td>
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<td>Use of LEF, n (%)</td>
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<tr>
<td>Current use</td>
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<td>Past use</td>
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<td>At the end of study</td>
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<td>Duration of biologic use, mean (s.d.), years</td>
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<td>Duration of follow-up, mean (s.d.), years</td>
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</tbody>
</table>

aQuestionnaires for reporting characteristics: prior to treatment assessment, 78 (18% = 78/422); initial assessment, 159 (38%); 6-month assessment, 80 (19%); 12-month assessment, 57 (14%); 18-month assessment, 30 (7%); 24-month assessment, 18 (4%). \(P\)-values were derived from the chi-squared test or analysis of variance. \(c\)At the time of biologic initiation. BASDAI: only available for 33 subjects.
after adjusting for baseline factors were present by time (or time + time²) in Table 3.

Mixed models showed that the difference between current smokers and non-smokers was −1.93 (95% CI −3.94, 0.09; P = 0.06) for the SF-36 physical score, −0.94 (95% CI −3.04, 1.16; P = 0.38) for the SF-36 mental score, −0.02 (95% CI −0.06, 0.02; P = 0.35) for the AQLoL score and 0.10 (95% CI −0.01, 0.20; P = 0.07) for the HAQ-S score after adjusting for gender, age, education, employment, co-morbidities, use of non-biologic DMARDs, NSAID use and analgesic drug use (Table 3). With additional adjustment of the BASDAI, the difference was 1.91 (95% CI −4.22, 0.40; P = 0.10), −0.50 (95% CI −2.92, 1.93; P = 0.69), −0.01 (95% CI −0.06, 0.04; P = 0.75) and 0.11 (95% CI −0.01, 0.23; P = 0.07) for SF-36 physical, SF-36 mental, AQoL and HAQ-S scores, respectively, in the subgroup of patients with the BASDAI measure.

In the mixed models, current smoking was not found to modify the effect of biologic DMARD treatment on HRQoL outcomes, as no interaction term between smoking status and time was statistically significant (all P-values > 0.36).

### Discussion

Smoking was not found to diminish or modify response to anti-TNF treatment in this study of Australian AS patients. Current smokers reported a similar level of improvement to biologic DMARD therapy to that of past smokers and non-smokers. However, the differences were not statistically significant. Also, the differences were unlikely to be of clinical relevance. The average reduction of 0.095 in the HAQ-S score is less than the minimal important difference (MID) for this score (0.14) in SpA patients. Although the MID in the SF-36 in AS patients has not been described, the average reduction reported in the SF-36 PCS of −1.93 in those who were current smokers was greater than the MID.
published in the literature for RA patients (MID of SF-36 PCS 2.6-4.4) [23].

Studies have linked smoking to poor HRQoL and diminished response to biologic DMARD treatment in patients with RA [4, 10]. Saevarsdottir et al. [10] reported that current smokers compared with non-smokers were less likely to achieve a good response according to the European League Against Rheumatism criteria at 3 months following the initiation of anti-TNF treatment (29% vs 43%; P = 0.03) in a study of 535 Swedish patients with early RA during 1996–2006. After adjusting for age, sex, past smoking, 28-joint DAS at diagnosis and use of prednisolone, DMARDs and MTX, the odds ratio of achieving a good response for current smokers compared with non-smokers was 0.52 (95% CI 0.29, 0.96) and the lower likelihood of a good response remained at 6 months.

It is not clear why there would be a differential in response modification of smoking seen between RA and AS, however, the inflammatory and immune responses of these conditions do vary, and this may simply reflect the fact that they are different patient groups. One hypothesis is that smoking influences radiographic progression, which is modified by biologic therapy in RA [24] but has not yet been shown to be modified by biologic therapy in SpA. The significant finding by Saevarsdottir et al. [10] could also be a result of their analyses, in which the influence of education level was not accounted for. Education is known to be associated with both smoking [25] and HRQoL [1]. In fact, the differences in SF-36 physical and HAQ-S scores between current smokers and non-smokers in our study would be statistically significant if education level was not included as a covariate in the regression models (data not shown).

Reports in the literature are mixed with respect to the impact of smoking on AS onset, disease activity and progression. An observational study of established AS patients (median disease duration 20 years) found no significant association between smoking status and either age at onset of disease or disease duration [26]. In contrast, a recent study of the DESIR (Devenir des Spondylarthropathies Indifférenciées Récents) cohort reported that in early AS patients, smoking was associated with earlier onset of inflammatory back pain [27]. Older studies of primarily established AS cohorts indicated that AS patients who were active smokers had significantly worse functional impairment as measured by the BASFI and the HAQ-S compared with non-smokers or past smokers [28–31]. Some more recent studies have reported that, in addition to functional impairment, current smokers also have higher disease activity [27, 32], while other studies have not found such an association [33–35]. New evidence is coming to light that current smoking has an impact on the progression of structural damage in the spine in patients with AS and anti-TNF treatment might reduce the progression, especially with early initiation [36–38]. Radiographs have not been collected systematically in the ARAD registry, so this question cannot be explored in our data.

Our study has several strengths and limitations. The sample size is large in comparison with other AS studies. Taking advantage of the panel structure of the ARAD data, a modern statistical method (mixed model) was employed to assess impacts of smoking on HRQoL measures. Thus the direction of the relationship is not a concern in this study as it would be in a cross-sectional study. Although the selected statistical method is capable of handling data that are missing completely or missing at random, we cannot be sure that this is the case for the missing data in this study. However, no difference in the rate of treatment failure was observed between subjects with different smoking status at the first data collection (P = 0.74). Also, the study patients may be systemically different from AS patients who were not in ARAD. Thus this study cannot adequately address issues related to confounding by indication resulting from selection bias. While the only disease-specific measure that was utilized in the database is the physical function HAQ-S, the other generic measures of HRQoL, including the SF-36, have been validated in AS patients.

In summary, this study does not indicate that smoking influences the improvement in quality of life following first anti-TNF therapy in AS patients. Although some quality of life indicators tend to be lower in active smokers than in non-smokers, the differences are neither statistically significant nor clinically important. In light of the contradiction of studies in RA patients where smoking does appear to influence treatment response, and recent evidence suggesting that smoking may influence radiographic progression in AS, further registry analyses among AS patients are warranted to confirm our findings.

### Rheumatology key messages

- Among AS patients, current smokers vs non-smokers tended to have poorer Short Form 36 physical and HAQ-S scores.
- Anti-TNF treatment improved health-related quality of life among AS patients for at least 2 years.
- The effects of anti-TNF treatment were not dependent on AS patients’ smoking status.

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