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ORIGINAL ARTICLE

Working life and physical activity in ankylosing spondylitis pre and post anti-tumor necrosis factor-alpha therapy

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Abstract

Aim: To assess effects of ankylosing spondylitis (AS) on working life and physical activity in Australia; to quantify changes in working life and physical activity that occur after anti-tumor necrosis factor-alpha (TNF-α) treatment; and to assess efficacy of anti-TNF-α therapy for AS in an Australian context.

Methods: This is a multi-centre observational study of people with AS on anti-TNF-α therapy. All participants satisfied the New York Modified Criteria and had active and refractory disease at anti-TNF-α therapy commencement. Participation involved a standardized interview, a metrology assessment, assessment of disease remission and medical record review. Interviews and patients' records were used to compare working life (employment, sick leave and productivity) and physical activity (participation rate, hours/week, and physical intensity) between the pre-AS, post-AS and post-anti-TNF-α therapy periods.

Results: Fifty-two patients took part. Participants were on average 44.8 years old, predominately male (86.5%) and had been on anti-TNF-α therapy for 29 months; 39% were in partial remission and 75% had 50% reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Responders to anti-TNF-α therapy were 10.5 years younger than non-responders ($P = 0.004$). Post-anti-TNF-α therapy participants gained 6.6 h/week of work ($P = 0.02$), and productivity improved 31% ($P < 0.001$) compared to immediately prior to commencing treatment. Physical activity participation increased from 71% to 85% ($P = 0.039$) and activity intensity increased by 33% ($P = 0.002$) post-treatment. Participants gained 1.8 h/week of sport ($P = 0.001$) and 2.2 h/week of recreational physical activity ($P < 0.001$).

Conclusions: Australians with AS have their working life and physical activity severely affected by this disease. Treatment with anti-TNF-α therapy results in significant improvement in these parameters.

Key words: ankylosing spondylitis, anti-TNF-α therapy, Australia, physical activity, productivity, sick leave, sport, working life.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease of the axial skeleton affecting 0.1–1.4% of Caucasian populations.[1,2] Classic symptoms include stiffness, back-pain and reduced spinal mobility.[1] Average age of onset is 24–26 years,[3] thus impacting on working life.

In Australia nearly 31% of people are affected by musculoskeletal diseases (MSD) and 2.8 million suffer lower back pain.[4] In the Western Pacific Region (WPR) of the WHO classification MSD currently contributes to 3.6% of total disability, as assessed by disability-adjusted life years.[5] This is estimated to increase to 4.2% by 2015 and 4.6% by 2030.[6] In the WPR-A

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region, which includes Australia, New Zealand, Japan and Singapore, MSD accounted for 11.3% of all years loss to disability.[5] Although AS was not individually analyzed by the WHO, with its early age of onset, it undoubtedly contributes to this disability.

Tumor necrosis factor-alpha (TNF-α) inhibitors were first approved for treatment of AS in Australia on 1 August 2004 and have revolutionized management.[1] Due to cost, strict criteria govern access to TNF-α inhibitors on the Australian Pharmaceutical Benefits Scheme (PBS). People with AS are required to be $\geq$ 18 years of age, under the care of a rheumatologist, exhibit AS (defined by the New York Modified Criteria) and have refractory and active disease (an elevated C-reactive protein [CRP] and/or erythrocyte sedimentation rate [ESR] and an Bath Ankylosing Spondylitis Disease Activity Index[7] [BASDAI] $\geq$ 4). To remain eligible for TNF-α inhibitors, patients must demonstrate an ongoing response by sustained reductions in CRP/ESR and BASDAI from baseline at 12 weeks after commencing treatment and every 6 months thereafter.

No data have been published regarding the effect of AS on working life in Australia. Employment status in AS significantly impacts on health-related quality of life.[8] Overseas data show that employment rates range from 34% to 96% and unemployment from 0.2% to 18% among those with AS[9]; 9.5% reduce their working hours, 8.4% change jobs and 20.2% retire early due to AS.[10] Productivity declines in 87%.[11] In 1998, productivity losses due to AS were calculated to cost €8862, €3609 and €3188 per patient in the Netherlands, Belgium and France, respectively.[12]

The effect of anti-TNF-α therapy on working life in AS is an area that has received limited attention to date. Overseas results suggest work hours increase (1.5 h/week),[13] sick-leave days fall (8.6–14.1 days/year)[13,14] and productivity improves (63%).[14] However, the rate of permanent disability remains unchanged.[15] This study investigates these phenomena in an Australian context.

The effect of AS on sport and recreational physical activity (RPA) has not been routinely assessed. A qualitative study noted several patients who exercised regularly prior to diagnosis had subsequently ceased or changed to less intensive activities,[16] while another noted a severe effect of fatigue on sport involvement.[17] A quantitative paper ranked sport fourth out of 38 patient concerns.[18] No research has quantified the decline in sport and RPA that occurs due to AS or analyzed changes that may occur after anti-TNF-α therapy. This paper attempts to do so. Given that AS affects a predominately young, healthy population, our hypothesis was that sport and RPA would be significantly affected by AS and that anti-TNF-α therapy may result in improvement in this area.

METHODS

This was a multi-centre retrospective observational study of 52 AS patients on PBS-subsidized anti-TNF-α treatment. Data were collected between August 2009 and January 2010. The study was conducted as an Independent Learning Project as part of the University of New South Wales (UNSW) Bachelor of Medicine, Bachelor of Surgery (MBBS) program. Approval for this study was obtained from the UNSW Medical and Community Human Research Ethics Advisory Panel. This study complies with the World Medical Association's Declaration of Helsinki.

This study was conducted in non-hospital rheumatology clinics in New South Wales. Eligible patients were informed in writing of the study and asked to return a stamped, addressed envelope. Non-responsive patients were followed up by telephone. Of the 66 patients contacted, 52 participated (78.8%). Participation involved review of medical records, a standardized interview, a metrology assessment, and assessment of disease remission. Informed consent was obtained from all participants.

Interview

Interviews were standardized and consisted of two parts. The first part involved closed-end questions regarding disease history, working life and physical activity. The second part (data not included in this study) involved open-ended questions and discussion of patient quality of life concerns specific to AS. All interviews were recorded and subsequently transcribed.

Participants' working lives were assessed in three time periods (before symptoms of AS, immediately before beginning anti-TNF-α therapy and during anti-TNF-α therapy). For each time period participants were specifically asked if they were working, and if so they were asked specifically about the nature of their work, the hours worked per week, the days of sick leave per year and their work productivity. Self-reported productivity was measured using a previously trialed 0–10 numerical rating scale (NRS).[14] Patient-reported results were cross-referenced with their medical notes from the relevant time period. Changes in hours worked, sick leave and productivity between the three time periods were evaluated using paired *t*-tests.

Like working life, physical activity was assessed in three time periods. Participants were questioned separately about sport and RPA. This division was made to identify the difference between competitive or team activities and less intense social/fun activities. Examples of each were given as prompts. Participants were specifically asked what activities they were doing regularly in each period, how long (in hours) and how often (per week) they performed them and how physically intense they were on a 0–10 NRS. From this data a total time per week for sport, RPA and all activities was calculated. McNemar tests were used to compare participation rates between time periods. McNemar's test was used in preference to Pearson's Chi-square tests as data were paired. Paired *t*-tests were used to compare activity length and intensity between periods.

Clinical assessment

Participants' Bath Ankylosing Spondylitis Metrology Index (BASMI)[19] and chest expansion were measured. The BASMI was calculated using an 11-point scale.[20] Participants were assessed for partial remission. Partial remission is one of several composite measures developed by the ASsessments in Ankylosing Spondylitis (ASAS) working group to standardize clinical assessment of anti-TNF-α efficacy.[21,22] It consists of four domains: patient global assessment; a visual analogue pain scale; the Bath Ankylosing Spondylitis Functional Index; and the last two components of the BASDAI. To achieve partial remission, patients must score ≤ 2 in each of these components.

Medical records

Participants' previous PBS applications were reviewed to extract all pre- and post-treatment BASDAI, CRP and ESR values. Post-treatment BASDAI scores were compared to pre-treatment valves to determine if a $\geq$ 50% reduction (BASDAI-50%)[23] was achieved.

Statistical analysis

Data was entered using Excel 2007 and converted to the Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). For normally distributed continuous data, a two-sample *t*-test was used except when the data was paired, where paired *t*-tests were used. McNemar's test were used in preference to a Chi-square test for comparing employment and participation rates between time periods as data was paired. In cases of independent qualitative data, a Chi-square test was used. In cases when a 2×2 contingency table had > 20% of cells with an expected value < 5, a Fisher's exact test was used in preference to a Chi-square test.[24,25] For correlations, a scatter plot was constructed to determine if the relationship between variables was linear, in which case a Pearson's correlation coefficient was calculated. For all results *P*-valves were taken to be significant when < 0.05 and highly significant when < 0.01.

RESULTS

Demographics

Analysis of 52 participants (Table 1) revealed the group was predominately male with an average age of 44.8 years. Of those with recorded human leukocyte antigen (HLA)-B27, 76.1% were positive. Average BASDAI, CRP and ESR immediately prior to beginning anti-TNF-α therapy were 7.97, 36 mg/L and 37 mm/h, respectively.

Participants had been on TNF-α inhibitors on average 29 months (range 3–71 months). Table 2 shows the utilization of the three anti-TNF-α agents available at the time of the study: 46%, 37% and 17% of partici-

Table 1 Demographic factors

Factor	Mean (± SD)	Range
Age	44.8 years (± 13.2)	21–75 years
Gender	86.5% male (45)	N/A
HLA-B27 status†	76.1% positive (35/46)	N/A
Family history‡	25.0% (13)	N/A
Smoking history	73.1% (38)	N/A
Age of onset	24.3 years (± 8.4)	12–44 years
Age at diagnosis	31.9 years (± 11.2)	16–61 years
Age at anti-TNF-α commencement	42.2 years (± 13.0)	19–75 years
Disease duration	20.5 years (+/− 13.1)	2–52 years
Delay to diagnosis	7.5 years (± 8.2)	0–34 years
Delay to anti-TNF-α treatment	18.3 years (± 12.9)	0–52 years
Length of anti-TNF-α treatment	29.4 months (± 19.1)	3–71 months
Baseline BASDAI§	7.97 (± 1.3)	4.91–10.00
Baseline CRP§	36.8 mg/L (± 36.2)	2.0–218.9 mg/L
Baseline ESR§	37 mm/h (± 24)	1–97 mm/h

†Results available for 46/52 participants. ‡Not independently verified in all cases. §Results available for 50 participants. HLA-B27, human leukocyte antigen B27; TNF, tumor necrosis factor; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2 Anti-TNF-α agents used

Agent	Initially (%)	Switched from (%)	Switched to	Currently (%)
Infliximab	9 (17.3)	5 (55.6)	3	7 (13.5)
Etanercept	19 (36.5)	2 (10.5)	5	22 (42.3)
Adalimumab	24 (46.2)	5 (20.1)	4	23 (44.2)

pants began on adalimumab, etanercept and infliximab, respectively. Twelve participants (23%) switched agents. Reasons for changing agents were: adverse reactions (4); difficulty accessing infliximab (3); no response to initial agent (2); recurrent uveitis (2); and recalcitrant enthesitis (1). Participants who began on infliximab infusions were significantly more likely to switch to another agent than those who started on a subcutaneous injection (Fisher's exact test; $P = 0.022$).

Peripheral arthritis was the most commonly experienced associated condition: 24 patients (46%). Twenty-two patients (42%) had a history of uveitis with three experiencing their first episode on anti-TNF-α therapy. Enthesitis, psoriasis, Crohn's disease, ulcerative colitis and rheumatoid arthritis had respective prevalencies of 19% (10 participants), 17% (9), 8% (4), 4% (2) and 4% (2).

Response to treatment

The average post-treatment BASMI score was 3.80 (range: 0–8.4) (Table 3). CRP and ESR were 12mg/L (range: < 1–186) and 11 mm/h (range: 1–50), respectively.

Twenty participants (39%) were in partial remission. Using an independent *t*-test, those in partial remission were statistically younger (10.5 years) ($P = 0.004$), had shorter disease duration (8 years) ($P = 0.03$) and were younger when anti-TNF-α therapy began (11.3 years) ($P = 0.002$). Those in partial remission were also more likely to be HLA-B27 positive (95% *vs*. 63%) (Fisher's exact test; $P = 0.013$) and have a family history of AS (40% *vs*. 16%)(Chi-square test; df = 1; test statistic = 3.900; $P = 0.048$). There were no significant differences in any of the pre-anti-TNF-α therapy mandatory measures (CRP, ESR, BASDAI) between those in remission and those not.

Thirty-nine participants (75%) had a BASDAI-50% reduction when interviewed and 37 (71%) exhibited this reduction at all time-points after commencing treatment. Using an independent *t*-test, participants who maintained a BASDAI-50% reduction were 12 years younger when beginning anti-TNF-α therapy (P =0.003) and 11.5 years younger overall ($P = 0.004$).

Table 3 Post-treatment metrology

Measure	Average (± SD)	Range	Average BASMI 11-point score (± SD)
Tragus to wall distance (cm)	17.3 (± 6.5)	9.25–30.50	2.92 (± 2.2)
Cervical rotation (degrees)	50.2 (± 25.4)	2.0–91.5	4.46 (± 3.1)
Intermalleolar distance (cm)	98.3 (± 31.3)	33–152	2.81 (± 2.8)
Lateral flexion (cm)	12.0 (± 7.1)	2.5–33.0	4.52 (± 3.0)
Modified Schober's test (cm)	4.5 (± 2.5)	0.3–10.0	4.27 (± 3.2)
BASMI score	3.80 (± 2.19)	0.00–8.40	N/A
Chest expansion (cm)	4.7 (± 2.5)	0.5–13.0	N/A

BASMI, Bath Ankylosing Spondylitis Metrology Index.

Again, there were no significant differences in initial CRP and ESR levels between the groups.

Working life

Before symptoms of AS, 39 participants (75%) were employed, working on average 46.9 h/week, taking 1.2 sick leave days/year and with productivity of 9.21 on a 10-unit scale (Table 4, Fig. 1). The remaining 13 were studying.

Immediately prior to beginning anti-TNF-α therapy, one participant was studying, 37 were working and 14 had stopped worked entirely. Twelve (23%) reported stopping as a direct result of AS, of whom 11 stated they had retired early due to AS with an average retirement age of 43.2 years (range: 24–73 years). These individuals estimated they had lost on average 16.5 years of working life (range: 2–36 years). Among the 37 working, nine (24%) had taken up a new job as a direct result of AS and another 10 (27%) had substantially changed their work practices due to AS.

Among the 37 working immediately prior to beginning anti-TNF-α therapy, h/week averaged 35.9, productivity rated 6.67 and sick leave was 11.3 days/year. Compared to before AS, this amounted to an 8.0 h/week reduction, 10.2 days/year increase and a 2.4 (26%) unit reduction, respectively. Using paired *t*-tests

Table 4 Employment status per time period

Time period	Employed	Studying	Looking for work	Retired due to AS	Retired for other reasons
Before AS	39	13	0	0	0
Before anti-TNF-α therapy	37	1	0	12	2
After anti-TNF-α therapy	40	0	5	5	2

AS, ankylosing spondylitis; TNF, tumor necrosis factor.

(n = 31) only the last of these changes was significant (t = 1.749, P = 0.09; t = –1.602, P = 0.121; t = 5.970, P < 0.001).

After anti-TNF-α therapy, of the 12 participants who had retired early due to AS, two had returned to work and another five were now looking for work. These seven were on average 25.9 years younger than the five who could still not work (37.9 *vs.* 63.8 years) (t = –5.592, P < 0.001).

After beginning anti-TNF-α therapy, those currently working averaged 42.4 h/week, 1.4 sick days/year and productivity of 8.75 out of 10. Using a paired t-test (n = 36), anti-TNF-α treatment resulted in a gain of 6.6 h/week (t = 3.395, P = 0.02) and a 31% increase in productivity (2.1 units) (t = 6.040, P < 0.001). The 9.9 days/year reduction in sick leave was not significant (t = −3.395, P = 0.073). Of the 40 participants now working, 34 (85%) reported anti-TNF-α therapy had a noticeable impact on work and they could now do more physically demanding tasks. Post-anti-TNF-α therapy, there was no significant difference in hours worked, sick leave or productivity when compared to the pre-AS level. Gains in productivity post-anti-TNF-α treatment correlated with the age at which anti-TNF-α therapy began (P = 0.001; Pearson's correlation coefficient = −0.547).

Physical activity

Participation

Fifty patients (96%) reported participating in some form of physical activity before AS, declining to 37 (71%) before anti-TNF-α therapy and rising to 45 (87%) after treatment (Table 5). Both these changes were significant (McNemar's test; P = 0.002 and P = 0.039, respectively). AS resulted in a significant reduction in participation in sport but not RPA (McNemar's test; P > 0.001, P = 0.263). Anti-TNF-α therapy resulted in a significant increase in participation in RPA but not sport (McNemar's test; P = 0.004, P = 0.057). There was a significant difference in sports participation

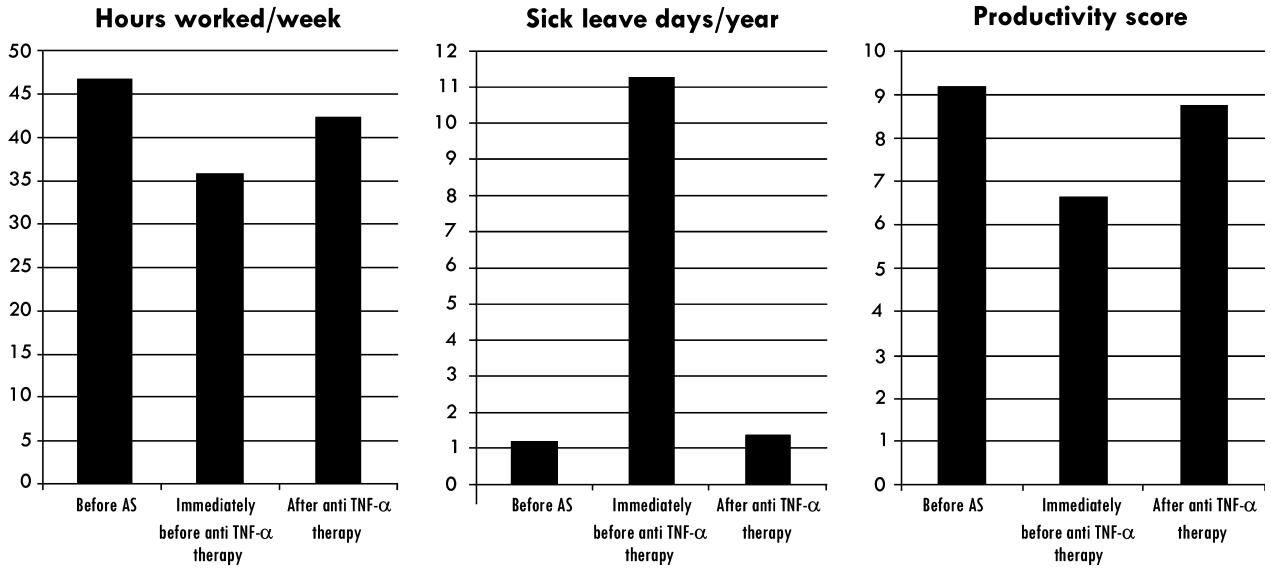

Figure 1 Hours worked, sick leave and productivity per time period.

Table 5 Physical activity before AS, after AS and after anti TNF-α treatment

	Before AS	Immediately prior to anti-TNF-α treatment	After anti-TNF-α treatment
Sport participation	84.6% (44)	28.8% (15)	44.2% (23)
Hours of sport/week/participant	7.2	0.8	2.6
Sport intensity	7.79	5.06	7.16
RPA participation	69.2% (36)	57.7% (30)	80.8% (42)
Hours of RPA/week/participant	5.1	2.2	4.4
RPA intensity	6.27	4.89	6.26
Total physical activity participation	96.2% (50)	71.2% (37)	86.5% (45)
Total hours of physical activity/week/participant	12.3	3.1	7.1
Total activity intensity	7.65	4.76	6.32

AS, ankylosing spondylitis; TNF, tumor necrosis factor; RPA, recreational physical activity.

when the period prior to AS was compared to after anti-TNF-α therapy (McNemar's test; $P < 0.001$).

Length and intensity of activity

Using a paired *t*-test, AS resulted in declines of 6.4 h/week of sport ($t = 7.204$, $P < 0.001$) and 2.8 h/week of RPA ($t = 2.392$, $P = 0.02$), giving a total decline of 9.2 h of physical activity per week ($t = 5.853$, $P < 0.001$). Physical intensity of all activities fell 2.52 units on a 10 unit scale (36%) ($t = 5.571$, $P < 0.001$).

Anti-TNF-α therapy resulted in a gain of 1.8 h/week of sport ($t = 3.411$, $P = 0.001$) and 2.2 h/week of RPA ($t = 4.289$, $P < 0.001$), giving an overall gain of 4.1 h/week of physical activity ($t = 5.428$, $P < 0.001$). Furthermore, those who started treatment earlier had bigger gains, with the age at which anti-TNF-α therapy began correlating to change in overall physical intensity and weakly correlating to change in total hours of physical activity (Pearson's correlation = −0.651, $P = 0.001$ and –0.462, $P = 0.001$, respectively). Average physical intensity of all activities improved 1.56 units (33%) when on anti-TNF-α therapy ($t = 3.537$, $P = 0.002$).

DISCUSSION

The aim of this study was to assess working life and physical activity in Australian AS patients and measure the change that occurred with anti-TNF-α therapy. In relation to physical activity, this study is the first to do this, as far as we are aware.

Anti-TNF-α treatment resulted in a gain of 6.6 h/week of work and a 31% increase in productivity. Most importantly, the second of these results correlated with the age at which anti-TNF-α treatment began. This is noteworthy given that lost productivity is the biggest cost associated with AS.[10] If starting those with AS on early treatment results in greater improvements in their work performance, it forms a very strong economic argument for making these agents more accessible earlier in the course of the condition. Strengthening this argument is the finding that among those who had stopped work due to AS, TNF-α inhibitors appeared to be most effective in returning younger people to work.

Generally the work gains post-anti-TNF-α therapy appear to be larger in Australia than those measured previously in European countries. In a British study participants were working 37.8 h/week before anti-TNF-α therapy and 39.3 h afterwards,[13] compared to 35.9 and 42.4 h respectively, in this study. This may be due to errors in participant reporting but suggests that TNF-α inhibitors in Australia may have a larger utility than previously estimated using foreign data.

The study has also clearly shown the impact of anti-TNF-α therapy on sport and RPA for those with AS. AS resulted in a 9.2 h/week decline in sport and RPA and TNF-α inhibitors produced a 4.1 h/week increase. Anti-TNF-α therapy also resulted in gains in participation rates (22%) and activity intensity (49%). The age at which anti-TNF-α treatment began weakly correlated with hours of total physical activity regained.

The retrospective nature of this study may reduce its validity. The study relied on participants to accurately recall details about their work and physical activity from various points in their life (prior to AS, immediately prior to beginning anti-TNF-α therapy and post-anti-TNF-α therapy). Additionally, it is possible that participants' subjective assessments of the effect of anti-TNF-α therapy may have influenced their reporting. Where possible, to limit inaccuracies, contemporaneous medical notes were cross-referenced.

The study provides a useful insight into AS in Australia. The average age of onset and delay to diagnosis (24.3 and 7.5 years, respectively) are very similar to the established literature,[2,3,26,27] validating the representativeness

of the study population. Participants were slightly more male (86.5%) than would be expected and female participants were on average 11 years older when diagnosed, suggesting that women with AS may still remain under-referred and/or under-diagnosed in Australia.

This study again confirmed that TNF-α inhibitors are effective at reducing disease activity, with 39% of participants in partial remission and 71% of participants experiencing a BASDAI-50% reduction at all time points after commencing therapy. Most importantly, responders were younger than non-responders. This confirms findings of a previous 5-year study.[28] Post-treatment BASMI scores were similar to those observed in a randomized controlled trial of anti-TNF-α agents.[29] Assessment of treatment response could have been improved by assessing more ASAS composite response criteria. However, in clinical practice, uptake of these additional measurements is poor.

There is now a growing body of evidence suggesting that the age at which anti TNF-α treatment begins may hold the key to prognosis. Patients who start treatment early may develop less spinal damage.[30] However, it is now also becoming clear that early treatment means better response to treatment.[30] This in combination with the larger work and physical activity gains experienced by younger patients, makes a strong case for a review of access to TNF-α inhibitors in Australia if other studies support these data.

Using the biopsychosocial model of health, any treatment that improves working life and physical activity may have flow-on benefits to all aspects of health.[31]

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AUTHOR CONTRIBUTIONS

All authors were involved in Concept and design or analysis and interpretation of data, Drafting and revising the study and Giving final approval for submission.

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