BMJ Open

Biologic Treatment Registry Across Canada (BioTRAC): a multicentre, prospective, observational study of patients treated with infliximab for ankylosing spondylitis

Proton Rahman,[1] Denis Choquette,[2] William G Bensen,[3,4] Majed Khraishi,[5] Andrew Chow,[6] Michel Zummer,[7,8] Saeed Shaikh,[9] Maqbool Sheriff,[10] Sanjay Dixit,[9] Dalton Sholter,[11] Eliofotisti Psaradellis,[12,13] John S Sampalis,[12,13] Vincent Letourneau,[14] Allen J Lehman,[14] François Nantel,[14] Emmanouil Rampakakis,[12,13] Susan Otawa,[14] May Shawi[14]

To cite: Rahman P, Choquette D, Bensen WG, *et al*. Biologic Treatment Registry Across Canada (BioTRAC): a multicentre, prospective, observational study of patients treated with infliximab for ankylosing spondylitis. *BMJ Open* 2016;**6**:e009661. doi:10.1136/bmjopen-2015-009661

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-009661).

Received 7 August 2015
Revised 5 November 2015
Accepted 10 December 2015

For numbered affiliations see end of article.

Correspondence to
Dr Proton Rahman;
prahman@mun.ca

ABSTRACT

Objectives: To describe the profile of patients with ankylosing spondylitis (AS) treated with infliximab in Canadian routine care and to assess the effectiveness and safety of infliximab in real world.

Setting: 46 primary care rheumatology practices across Canada.

Participants: 303 biological-naïve patients with AS or patients previously treated with a biological for <6 months and who were eligible for infliximab treatment as per routine care within the Biologic Treatment Registry Across Canada (BioTRAC).

Intervention: Not applicable (non-interventional study).

Primary and secondary outcomes: Effectiveness was assessed with changes in disease parameters (AS Disease Activity Score (ASDAS), Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), Health Assessment Questionnaire Disease Index (HAQ-DI), physician global assessment of disease activity (MDGA), patient global disease activity (PtGA), back pain, C-reactive protein, erythrocyte sedimentation rate (ESR), morning stiffness). Safety was assessed with the incidence of adverse events (AEs).

Results: Of the 303 patients included, 44.6% were enrolled in 2005–2007 and 55.4% in 2008–2013. Patients enrolled in 2005–2007 had significantly higher MDGA and ESR at baseline while all other disease parameters examined were numerically higher with the exception of PtGA. Treatment with infliximab significantly ($p<0.001$) improved all disease parameters over time in both groups. At 6 months, 56% and 31% of patients achieved clinically important (change≥1.1) and major (change≥2.0) improvement in ASDAS, respectively; at 48 months, these proportions increased to 75% and 50%, respectively. Among patients unemployed due to disability at baseline, 12.1% returned to work (mean Kaplan-Meier (KM)-based time=38.8 months). The estimated retention rate at 12 and 24 months was 78.3% and 60.1%, respectively. The profile and incidence of AEs were comparable to data previously reported for tumour necrosis factor-α inhibitors.

Conclusions: Characteristics of patients with AS at infliximab initiation changed over time towards lower disease activity and shorter disease duration. Infliximab treatment significantly reduced disease activity independent of treatment initiation year, although patients enrolled in recent years achieved lower disease activity over 48 months.

Trial registration number: NCT00741793.

Strengths and limitations of this study

- To our knowledge, this is the first study assessing the burden of illness of ankylosing spondylitis in a real-world setting in Canada.
- The large number of patients seen in a real-world setting during routine clinical practice enhances the generalisability of the data to the target population.
- Examination of radiographic progression was not possible as radiographic images are not collected in Biologic Treatment Registry Across Canada (BioTRAC).
- Completer analysis was used for the assessment of clinical and patient outcomes; therefore, the treatment effect may have been overestimated because of the healthy worker effect.
- Safety was assessed with the incidence of physician and patient-reported adverse events at every follow-up which may have led to underestimated rates due to patient recall bias.

INTRODUCTION

Ankylosing spondylitis (AS) is the prototype of spondyloarthropathies (SpA), a group of

diseases presenting with inflammation of the axial skeleton, peripheral arthritis and enthesitis (inflammation at insertion site of tendons, ligaments and joint capsules).[1] Extra-articular manifestations of AS include inflammatory bowel disease, anterior uveitis and psoriasis.[2] The disease generally manifests in the second to third decade of life.[3 4] The prevalence of AS is estimated to be as high as 0.9% and affects between 150 000 and 300 000 people in Canada.[5] Studies have shown that AS is associated with a significant economic burden which is directly associated with disease severity, in particular deteriorating physical function.[6–9] Compared with the general population, individuals with AS have lower employment rates, experience more disability and are more frequently absent from work.[10–12]

Currently, there is no cure for AS, but early diagnosis and treatment may control the clinical symptoms and minimise joint damage.[13] Traditional therapies, including non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy have been the mainstay for treatment of AS.[14] Although these therapies remain the first-line treatment option, a substantial proportion of patients cannot be sufficiently treated with NSAID therapy alone.[15] Similarly, despite the efficacy of disease-modifying anti-rheumatic drugs (DMARDs) in rheumatoid arthritis (RA), their impact on disease progression is only modest in patients with axial SpA, particularly those with AS.[16 17] Apart from NSAIDs and physiotherapy, no therapeutic agent with proven efficacy in AS was available until the introduction of antitumour necrosis factor α (TNF-α) agents. Treatment with infliximab (IFX), an anti-TNF-α agent, has been shown to result in significant improvements in disease activity (Bath AS Disease Activity Index, BASDAI), functional index (Bath AS Functional Index, BASFI) and spinal mobility (Bath AS Metrology Index, BASMI).[18–21] Moreover, the clinical efficacy of IFX has been substantiated by magnetic resonance imaging (MRI) studies showing a clear reduction in acute inflammation in the spine and sacroiliac joints.[19 22 23]

Although the salient features of diagnostic criteria for AS are radiographic sacroiliitis and symptoms and signs of axial arthritis, this is problematic because structural changes may only become apparent after 6–8 years of disease activity.[24–28] Furthermore, MRI is not recommended for the assessment of back pain in routine care due to its high cost.[29] This diagnostic delay may result in a decreased effectiveness to TNF-α inhibitors, where disease duration has been established as a predictor of response.[30]

A paucity of literature exists discussing the efficacy and tolerability of anti-TNF-α in routine clinical practice. Post-approval clinical studies allow the assessment of the real-world effectiveness of treatments on the target population treated under routine care. Moreover, ongoing long-term surveillance for safety signals under routine clinical practice is necessary for the detection of rare, but potentially serious adverse events (SAEs). Using data from the Biologic Treatment Registry Across Canada (BioTRAC), the current analysis describes the profile of patients with AS over time treated with IFX in Canada and describes the effectiveness and the safety of IFX in routine clinical practice.

METHODS

Study design

BioTRAC is an ongoing prospective, multicentre, observational registry collecting real-world clinical, laboratory, patient-centric and safety data in patients with RA, AS and psoriatic arthritis treated with IFX or golimumab (GLM) as part of their routine care. The historical development of the registry has been described by Thorne *et al*.[31] To date, there are over 70 rheumatology sites participating, both in an institutional and private setting, with over 1800 patients enrolled in the programme across all indications. In accordance with the observational nature of the registry, there is no protocol-defined intervention in the patient management and all clinical decisions, including anti-TNF initiation, and treatments are based on routine practice and the judgement of the treating physicians. Patients provided written informed consent prior to participation in the study. Ethics approvals for participation in the BioTRAC program were obtained from the respective Research Ethics Boards (REB) of participating institutional sites and a Central Institutional Review Board (IRB Services, Ontario Canada) for private practice sites. BioTRAC is conducted according to the tenets of the Declaration of Helsinki.

Study population

Biological-naïve patients or patients previously treated with a biological for <6 months and who are eligible for treatment with IFX or GLM as per the Canadian Product Monograph are considered for inclusion in the registry. For the purpose of the current analysis, patients with AS who initiated treatment with IFX between 2005 and 2013 were included. In order to examine differences in patient characteristics over time, the cohort was divided in two almost equal subgroups, those enrolled between 2005 and 2007 vs those enrolled between 2008 and 2013. All effectiveness analyses were performed in the modified intent-to-treat (mITT) population comprising all enrolled patients who received at least one dose of IFX and had at least one follow-up assessment (N=303). Safety analysis was based on the safety population including all patients who received at least one dose of IFX (N=320).

Data collection

The following clinical parameters and patient-reported outcomes were collected by the treating physician: morning stiffness, AS Disease Activity Score (ASDAS), BASDAI, BASFI, Health Assessment Questionnaire Disease Index (HAQ-DI), physician global assessment of

disease activity (MDGA), patient global disease activity (PtGA), back pain, C-reactive protein (CRP) value and erythrocyte sedimentation rate (ESR) value. PtGA and back pain were based on the Assessment of SpondyloArthritis International Society (ASAS) core set. Safety was assessed with the incidence of AEs.

Statistical analysis

Descriptive statistics including measures of central tendency (mean, median) and dispersion (SD, 95% CIs of the mean) were presented for continuous patient characteristics and clinical outcome measures. Frequency distributions were produced for categorical variables.

Table 1 Patient demographics and baseline characteristics

Parameter	Enrolment period 2005–2007 N=135	Enrolment period 2008–2013 N=168	Total N=303	p Value* (between groups)
Demographics				
Male gender, n (%)	82 (60.7)	107 (63.7)	189 (62.4)	0.634
Age, years, mean (SD)	45.6 (11.6)	45.7 (11.9)	45.6 (11.7)	0.958
Baseline characteristics				
Disease duration, years, mean (SD)	11.1 (10.8)	8.2 (9.2)	9.6 (10.0)	*0.011*
Unemployed, n (%)†	62 (45.9)	77 (46.7)	139 (46.3)	0.908
Unemployed due to disability, n (%)‡	29 (46.8)	37 (48.1)	66 (47.5)	>0.999
Financial coverage, n (%)†				
Public	38 (28.1)	67 (41.9)	105 (35.6)	*0.012*
Private	71 (52.6)	70 (43.8)	141 (47.8)	
Public and private	10 (7.4)	16 (10.0)	26 (8.8)	
Other	16 (11.9)	7 (4.4)	23 (7.8)	
IFX dose (mg/kg), mean (SD)	4.3 (1.0)	4.4 (1.2)	4.4 (1.1)	0.372
Number of previous DMARDs, mean (SD)	0.7 (1.1)	0.5 (0.8)	0.6 (0.9)	0.078
Previous therapy, n (%)				
DMARDs	56 (41.5)	56 (33.3)	112 (37.0)	0.152
NSAIDs	97 (71.9)	125 (74.4)	222 (73.3)	0.695
Corticosteroids	37 (27.4)	46 (27.4)	83 (27.4)	>0.999
Methotrexate	33 (24.4)	40 (23.8)	73 (24.1)	0.894
Concomitant therapy, n (%)				
DMARDs	37 (27.4)	50 (29.8)	87 (28.7)	0.702
NSAIDs	72 (53.3)	99 (58.9)	171 (56.4)	0.352
Corticosteroids	9 (6.7)	6 (3.6)	15 (5.0)	0.288
Methotrexate	28 (20.7)	41 (24.4)	69 (22.8)	0.492
NSAIDs, previous or concomitant therapy, n (%)	116 (85.9)	130 (77.4)	246 (81.2)	0.075
ASDAS, mean (SD)	3.9 (0.9)	3.7 (1.1)	3.8 (1.0)	0.103
ASDAS disease activity, n (%)†				
Inactive (<1.3)	0 (0.0)	4 (3.1)	4 (1.7)	0.160
Moderate (1.3–2.0)	1 (1.0)	3 (2.3)	4 (1.7)	
High (2.1–3.5)	34 (33.0)	50 (38.5)	84 (36.1)	
Very high (>3.5)	68 (66.0)	73 (56.2)	141 (60.5)	
BASDAI, mean (SD)	6.5 (1.9)	6.4 (2.2)	6.4 (2.0)	0.490
BASFI, mean (SD)	6.3 (2.2)	6.1 (2.5)	6.2 (2.4)	0.447
HAQ-DI, mean (SD)	1.3 (0.6)	1.2 (0.6)	1.2 (0.6)	0.318
AM stiffness§, minutes, mean (SD)	79.0 (38.9)	70.1 (42.4)	74.1 (41.0)	0.064
MDGA (NRS: 0–10), mean (SD)	7.0 (1.6)	6.3 (2.1)	6.6 (1.9)	*0.001*
PtGA (NRS: 0–10), mean (SD)	6.6 (2.3)	6.7 (2.4)	6.7 (2.3)	0.811
Back pain (NRS: 0–10), mean (SD)	6.7 (2.5)	6.5 (2.6)	6.6 (2.6)	0.623
ESR (mm/h), mean (SD)	30.0 (23.1)	19.9 (18.1)	24.5 (21.1)	*<0.001*
CRP (mg/L), mean (SD)	20.4 (23.9)	16.7 (25.7)	18.3 (24.9)	0.243

*Statistically significant values are marked in italics.
†Percentages based on patients who provided a response: employment (n=300); financial coverage (n=295); ASDAS disease activity (n=233).
‡Percentage based on total number of unemployed patients (n=139).
§Capped at 120 min.
AM stiffness, morning stiffness; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disease Index; IFX, infliximab; MDGA, physician global assessment of disease activity; NRS, Numeric Rating Scale; NSAIDs, non-steroidal anti-inflammatory drugs; PtGA, patient global disease activity.

Between-group differences in patient baseline characteristics and demographics across enrolment periods were assessed for statistical significance using the χ^2 statistic for categorical parameters and the independent-samples t test for continuous parameters. Within-group improvements in continuous disease parameters over time were assessed with linear mixed-effects models. The Kaplan-Meier (KM) estimator of the survival function was used to assess the durability of the treatment and time to employment; comparisons between subgroups were made with the log-rank test. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA V.13.0) and summarised using the total number of AEs, the total number and percentage of patients who experience an AE overall and by body system and preferred term. AE relationship to the study medication was based on the judgement of the treating physician. All statistical tests were two-sided, with a p value of 0.05 or less considered to indicate statistical significance. Statistical analyses were conducted with SPSS V.12.0 (SPSS Inc, Chicago, Illinois, USA) and SAS V.9.2 (SAS Institute, Cary, North Carolina, USA).

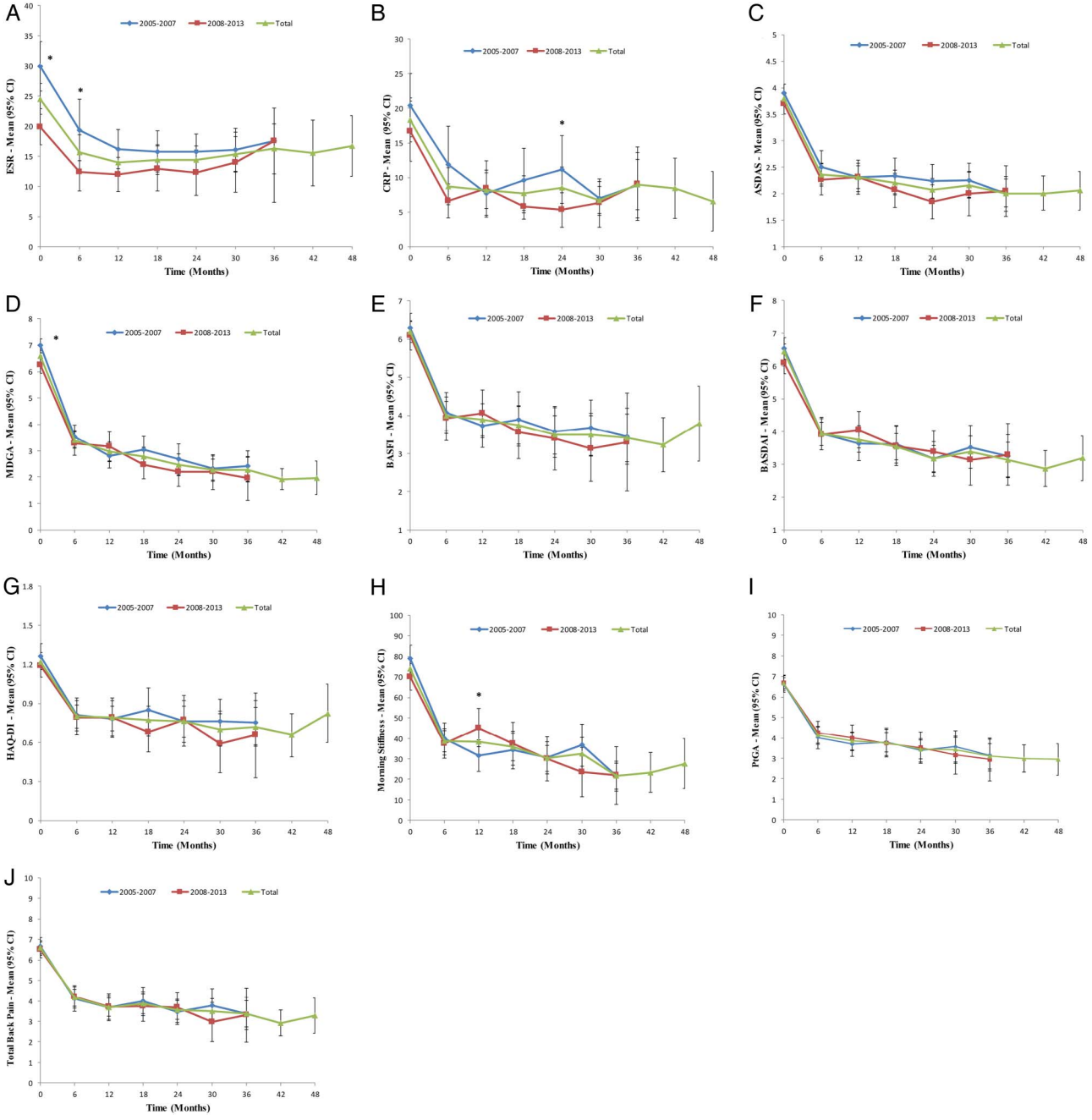

Figure 1 Disease parameters over time. The total number of patients attending the 6-month, 12-month, 18-month, 24-month, 30-month, 36-month, 42-month and 48-month assessment was 215, 167, 136, 116, 97, 74, 52 and 38, respectively. *Denotes statistically significant difference between subgroups.

RESULTS

Patient demographics, characteristics and treatment parameters

A total of 303 patients with AS were included in the mITT population. Patient demographics and baseline characteristics are summarised in table 1 for the total cohort and by enrolment period (2005–2007 and 2008–2013). There were 189 (62.4%) males, mean (SD) age was 45.6 (11.7) years and mean (SD) disease duration was 9.6 (10.0) years. Patients recruited in recent years had significantly lower disease duration (8.2 vs 11.1 years; p=0.011). At baseline, 139 (46.3%) of patients were unemployed. Among these, disability was the predominant reason for unemployment (47.5%), while other reasons included retirement (18.7%), being a homemaker (8.6%), or a student (4.3%), and temporary leave of absence (4.3%). A significant relationship was observed between financial coverage and enrolment period (p=0.012), with public coverage being significantly higher (41.9% of patients) in the 2008–2013 enrolment period relative to 2005–2007 (28.1% of patients).

Previous use of NSAID, DMARD, corticosteroid and methotrexate therapy was reported by 73.3%, 37.0%, 27.4% and 24.1% of patients, respectively. At IFX initiation, 56.4%, 28.7%, 22.8% and 5.0% of patients were treated with concomitant NSAIDs, DMARDs, methotrexate and corticosteroids, respectively. Furthermore, previous or concomitant use of NSAIDs was reported by 81.2% of patients. No significant differences were observed for previous and concomitant therapy use between enrolment periods.

Overall, baseline disease parameters were numerically lower for the most recent enrolment period (2008–2013) relative to the first period (2005–2007), with the

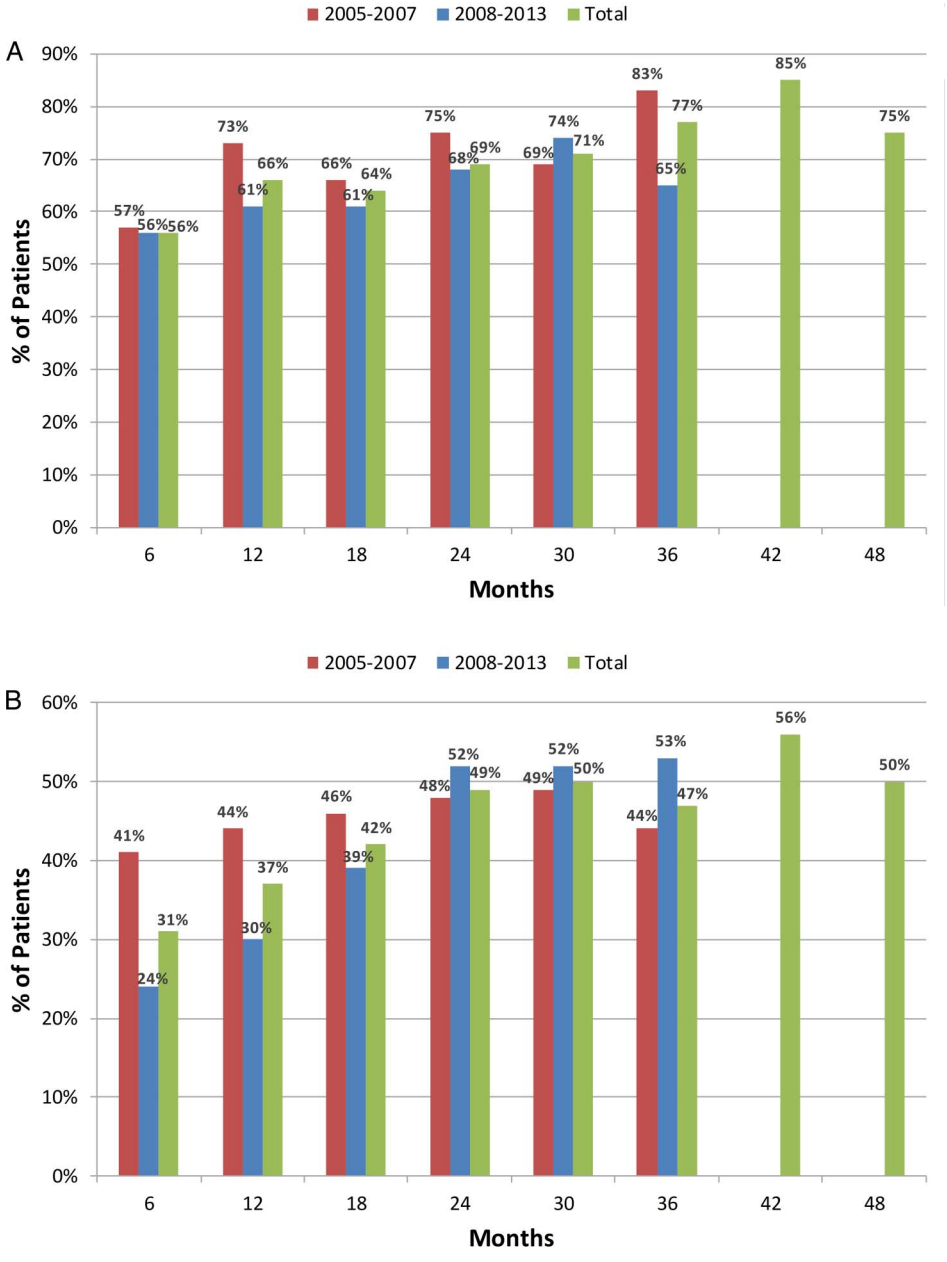

Figure 2 (A) Ankylosing Spondylitis Disease Activity Score (ASDAS) clinically important improvement over time. (B) ASDAS major improvement over time. The percentages are based on completers.

following parameters showing a statistical difference between the two groups: ESR (19.9 vs 30.0 mm/h; p<0.001), MDGA (6.3 vs 7.0; p=0.001). No significant differences were observed for BASDAI, BASFI, HAQ-DI, PtGA, back pain and CRP between enrolment periods.

In the overall population, the majority of patients had very high (60.5%), or high (36.1%), ASDAS disease activity at baseline.

Effectiveness outcomes

The disease parameters over 48 months of treatment with IFX are summarised in figure 1. Statistically significant (p<0.001) and clinically meaningful improvement was observed for all disease parameters evaluated including ESR, CRP, ASDAS, BASFI, BASDAI, HAQ-DI, MDGA, PtGA, back pain and morning stiffness at 6 months of treatment and was further sustained over 48 months. Regression analysis showed that patients enrolled in 2008–2013 had significantly lower disease activity over time compared with those enrolled in 2005–2007 as indicated by the statistically lower ESR (p<0.001; figure 1A), CRP (p=0.027; figure 1B), ASDAS (p=0.046; figure 1C) and MDGA (p=0.012; figure 1D). No significant differences in BASFI (figure 1E), BASDAI (figure 1F), HAQ-DI (figure 1G), morning stiffness (figure 1H), PtGA (figure 1I) and back pain (figure 1J) were observed over time between enrolment periods. By 6, 12, 24, 36 and 48 months, 56%, 66%, 72%, 77% and 75%, respectively, of patients achieved clinically important improvement in ASDAS (change ≥1.1; figure 2A); major improvement (change ≥2.0) in ASDAS was achieved by 31%, 37%, 49%, 47% and 50%, respectively. No statistically significant differences were observed between the two groups in terms of meeting ASDAS end points. Achievement of ASDAS major improvement was faster within the earlier enrolment period (figure 2B) which could be due to the higher baseline ASDAS in this group.

The proportion of patients employed at baseline was 53.7%. Of these patients, 3 (1.9%) patients became unemployed due to disability during the course of the follow-up. Among patients unemployed due to disability at baseline, 8 (12.1%) patients returned to work after a mean (95% CI) KM-based time of 38.8 (33.2–44.4) months.

Discontinuations, safety and tolerability

A total of 320 patients received at least one dose of IFX and were included in the safety population. After an average of 19.3 months of follow-up, 104 (32.5%) patients discontinued from the study. Reasons for discontinuation included: lack/loss of response (n=34; 10.6%), AE (n=28; 8.8%), loss to follow-up (n=11; 3.4%), withdrawal of consent (n=10; 3.1%), geographic issues (n=6; 1.9%), disease progression (n=4; 1.3%), patient received other therapy (n=4; 1.3%), financial reasons (n=3; 0.9%), complete response (n=2; 0.6%) and other (n=2; 0.6%). Using survival analysis, mean (95% CI) time to discontinuation was 43.0 (38.7–47.3)

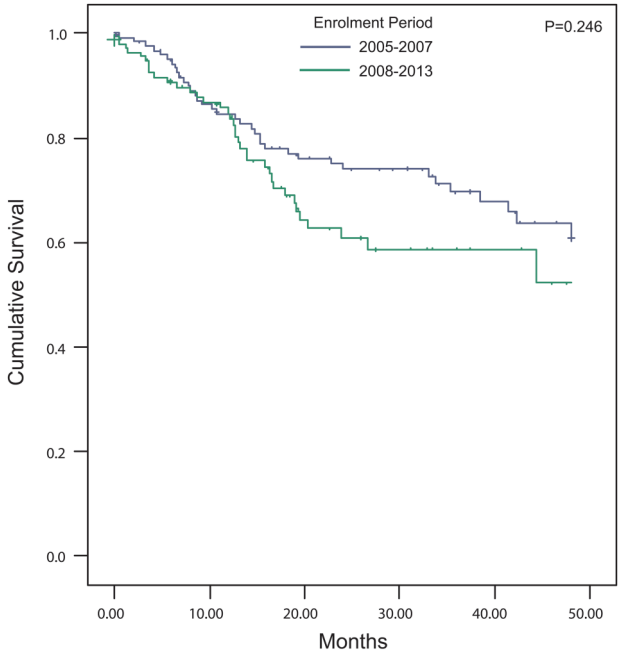

Figure 3 Treatment survival.

months for the total cohort, with a probability of retention of 78.3% and 60.1% at 12 and 24 months, respectively, and time to discontinuation due to lack/loss of response, disease progression, AE or change in therapy was 50.6 (46.3–55.1) months. No significant differences between enrolment periods were observed (figure 3). However, concomitant use of methotrexate was associated with significantly higher durability of IFX treatment (HR (95% CI) 0.63 (0.41 to 0.95)).

A total of 1153 AEs were reported by 175 (54.7%) patients, the majority of which 1107 (96.0%) were non-serious as per the judgement of the treating physician. Table 2 describes AEs occurring in ≥2% of patients. The most frequently reported AEs were arthralgia (8.1% of patients), back pain (7.5%), nasopharyngitis (6.9%) and pain in extremities (5.9%). Infusion-related reactions were reported for 2.9% of patients. Overall, no significant differences in the profile and incidence of AEs was observed between enrolment periods with the exception of pain (7.9% vs 1.7%; p=0.016) and neck pain (7.9% vs 1.1%; p=0.006), which were higher in the 2005–2007 enrolment period.

A total of 43 SAEs were reported for 26 (8.1%) patients (table 3); 23 SAEs occurred for patients enrolled in the 2005–2007 period and 20 occurred in the 2008–2013 enrolment period. There were two serious infections, one was a kidney infection and the other was a urinary tract infection both occurring in the 2008–2013 enrolment period. No tuberculosis cases or malignancies were observed.

DISCUSSION

The goals of this study were to describe the profile of patients with AS treated with IFX between 2005–2007

Table 2 AEs occurring in ≥2% of patients—safety population

Preferred term*	Enrolment period 2005–2007 Percent of patients†	2005–2007 Number of AEs	2008–2013 Percent of patients†	2008–2013 Number of AEs	Total Percent of patients†	Total Number of AEs
Total	56.4	650	53.3	503	54.7	1153
Arthralgia	9.3	30	7.2	35	8.1	64
Back pain	9.3	33	6.1	18	7.5	51
Pain in extremity	6.4	18	5.6	21	5.9	39
Nasopharyngitis	8.6	20	5.6	14	6.9	34
Fatigue	6.4	23	2.2	5	4.1	28
Neck pain	7.9	20	1.1	3	4.1	23
Sinusitis	5.0	14	6.1	8	5.6	22
Hypoaesthesia	5.0	10	2.8	12	3.8	22
Nausea	4.3	13	2.8	8	3.4	21
Pain	7.9	18	1.7	3	4.4	21
Upper respiratory tract infection	5.7	12	3.9	7	4.7	19
Diarrhoea	3.6	5	4.4	13	4.1	18
Headache	5.0	10	3.9	8	4.4	18
Pruritus	4.3	9	3.9	9	4.1	18
Rash	5.7	13	1.7	4	3.4	17
Oropharyngeal pain	3.6	13	1.7	3	2.5	16
Infusion-related reaction	3.6	6	2.2	9	2.8	15
Chest pain	2.1	6	2.8	8	2.5	14
Dyspepsia	2.9	9	1.7	5	2.2	14
Hepatic enzyme increased	2.1	4	3.9	10	3.1	14
Urinary tract infection	3.6	7	2.2	7	2.8	14
Cough	2.1	3	3.9	10	3.1	13
Pharyngitis	4.3	6	2.2	7	3.1	13
Musculoskeletal stiffness	1.4	5	2.8	7	2.2	12
Uveitis	2.9	7	2.2	5	2.5	12
Gastroenteritis	5.7	9	1.1	2	3.1	11
Influenza	5.7	8	1.7	3	3.4	11
Fever	3.6	8	1.1	2	2.2	10
Vomiting	2.9	4	3.3	6	3.1	10
Fall	2.9	4	1.7	5	2.2	9
Hypertension	4.3	7	1.1	2	2.5	9
Ear infection	2.9	4	1.7	3	2.2	7

*MedDRA V.13.0.
†Patients experiencing the same AE or SAE multiple times were only counted once for the corresponding preferred term.
AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; SAEs, serious adverse events.

and 2008–2013 and to assess the effectiveness and the safety of IFX in routine clinical practice over a 48-month period. Mean (SD) disease duration at IFX initiation in the current study was 9.6 (10.0) years which is comparable with that reported in the Anti-TNF Treatment of RA (ATTRA) registry (8.1 (6.9) years).[32] Other biological treatment registries, such as Turkey's Turkiye Romatizma Arastirma Savas Dernegi-Izlem Programi (TRASD-IP),[33] Spain's national registry of spondyloarthropathies (REGISPONSER),[25] Denmark's Danish Rheumatologic Database (DANBIO)[34] and Czech Republic's ATTRA[32] have reported disease durations that varied from 5.0[35] to 15.5 years.[36 37] One-year and 2-year retention was 78.3% and 60.1%, respectively, which is comparable with the first course biological retention rate reported for the DANBIO registry (2-year retention: 58%) but lower than that reported for ATTRA (1-year retention: 84%; 2-year retention: 76%).[32 34] These differences could possibly be attributed in differences in patient management such as the concomitant use of methotrexate which was identified as a predictor of improved IFX treatment durability. This association has been previously shown and might be due to the improved persistence with anti-TNF treatment in patients with AS treated concomitantly with DMARDs previously described.[38 39]

Subgroup analysis by enrolment period showed that the profile of patients initiating treatment with IFX in Canadian routine care has changed towards less severe disease, shorter disease duration and lower number of prior DMARDs in recent years. The shorter disease duration in the recent enrolment period may be due to changes in patient management involving the earlier initiation of biologicals or an overall increased awareness

Table 3 SAEs of interest—safety population

Preferred term*	Total	
	Percent of patients†	Number of SAEs
Total	8.1	43
Abdominal pain	0.3	1
Aortic aneurysm	0.3	1
Arthralgia	0.3	1
Arthritis	0.3	1
Atrial fibrillation	0.3	1
Back pain	0.3	1
Breast hyperplasia	0.3	1
Cerebrovascular accident	0.3	1
Chest discomfort	0.3	2
Chest pain	0.3	1
Concussion	0.3	1
Coronary artery bypass	0.3	1
Depression	0.3	1
Dyspnoea	0.3	1
Fall	0.3	1
Gastrointestinal inflammation	0.3	1
Hip arthroplasty	0.3	1
Hot flush	0.3	1
Infusion-related reaction	0.3	1
International normalised ratio increased	0.3	1
Interstitial lung disease	0.3	1
Intestinal obstruction	0.6	2
Kidney infection	0.3	1
Myocardial infarction	0.3	1
Nephrolithiasis	0.3	1
Neuropathy peripheral	0.3	1
Ovarian cyst ruptured	0.3	1
Pleural effusion	0.3	1
Pneumothorax	0.3	1
Pulmonary mass	0.3	1
Fever	0.3	1
Rash	0.3	1
Rash erythematous	0.3	1
Rash pruritic	0.3	1
Rectal haemorrhage	0.3	2
Skin cyst excision	0.3	1
Thrombophlebitis	0.3	1
Urinary tract infection	0.3	1
Uveitis	0.3	1
Vomiting	0.3	1

*MedDRA V.13.0.
†Patients experiencing the same AE or SAE multiple times were only counted once for the corresponding preferred term.
AEs, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; SAEs, serious adverse events.

leading to earlier AS diagnosis. Although between-group differences were not observed for gender, the proportion of females was higher than expected given that previous studies have demonstrated that AS predominantly affects males at a ratio of 3:1.[40 41] The frequency of concomitant DMARD therapy was relatively low (28.7%) and comparable between enrolment periods which is in line with previous studies showing that their impact on disease progression is only modest in patients with axial SpA, particularly those with AS.[16 17] Treatment resulted in lower disease activity over 48 months in patients enrolled between 2008 and 2013 suggesting that patients may benefit from earlier treatment with IFX. Treatment with IFX for 6 months resulted in significant improvement in all outcomes which was further sustained until 48 months. With respect to BASDAI, the REGISPONSER registry showed similar improvements assessed over a period of <5 years.[25] The change in BASFI, BASDAI and MDGA during the first 6 months of treatment was also in line with the results observed in the studies conducted by Glintborg *et al*[34] and Haibel *et al*,[36] where participants were similarly treated with biological drugs. The Czech national registry showed comparable results in terms of baseline BASDAI, BASFI, HAQ and CRP disease parameters; over 36 months of treatment, the mean (SD) change in BASDAI of 3.0 (2.5) and CRP level of 7.5 (16.2) mg/L were also in line with our results over the same time period.[32] IFX resulted in clinically important improvements for ASDAS, with an increase in the percentage of responders increasing from 56% at 6 months to 75% at 48 months. The increased rate of major ASDAS improvement observed in the first 12 months of treatment in patients in the earlier enrolment period could possibly be explained by the higher baseline disease activity in this population.

In the present study, the unemployment rate at baseline was 47.5% which was similar to that reported in a large cohort study conducted in the UK (40%).[42] Other European studies have shown that unemployment rates among patients with AS can range from 15% to 45%.[4 43–45] The literature has also reported that work disability rates ranged from 3% after 8 years to 50% after 45 years of disease in patients with AS.[43] During the course of our study, a low rate (1.9%) of patients became unemployed due to disability while on IFX treatment; while 12.1% of patients who were unemployed due to disability at baseline returned to work. From a socioeconomic perspective, early initiation of IFX could have implications on the economy, use of healthcare resources and indirect costs associated with physical impairment.[4 43 46]

IFX was generally well tolerated by patients with AS in the current study. The incidence of AEs and SAEs was comparable across enrolment periods, with the exception of pain which was more common in the earlier enrolment period. Serious infections occurred in 0.3% of patients. No tuberculosis cases or malignancies were observed. The incidence of AEs was lower relative to what has been reported in other studies.[47 48] The lower incidence rate of AEs in this study may have been caused by patient recall bias given the longer interval between follow-up assessments as compared with randomised controlled trials.

Treatment retention was high with 32.5% of patients discontinuing treatment after 43 months. Treatment discontinuation due to lack/loss of response or disease

progression was 11.9% while 8.8% were discontinued due to an AE.

Our study has certain limitations. Although several approaches were used to assess disease activity, radiographic images are not collected in BioTRAC, thus not allowing the examination of radiographic progression. In addition, completer analysis was used for the assessment of clinical and patient outcomes; therefore, the treatment effect may have been overestimated because of the healthy worker effect. Safety was assessed with the incidence of physician and patient-reported AEs at every follow-up which may have led to underestimated rates due to patient recall bias. A strength of the study, however, is the large number of patients seen in a real-world setting during routine clinical practice which enhances the generalisability of the data to the target population.

In conclusion, the results of the current study suggest that characteristics of patients with AS at initiation of IFX and patient management by the treating physicians have changed over time. Treatment with IFX was well tolerated and effective in improving clinical parameters, patient-reported outcomes and patient ability to work. Early diagnosis and treatment initiation at the early stages of the disease process may be beneficial in terms of clinical response and patient-reported outcomes which may have significant economic implications.

Author affiliations
[1]Department of Medicine & Rheumatology, Memorial University, St. John's, Newfoundland, Canada
[2]Institut de Rhumatologie de Montréal, Montreal, Quebec, Canada
[3]St. Joseph's Hospital, Hamilton, Ontario, Canada
[4]McMaster University, Hamilton, Ontario, Canada
[5]Memorial University of Newfoundland, St. John's, Newfoundland, Canada
[6]Credit Valley Rheumatology, Mississauga, Ontario, Canada
[7]Université de Montréal, Montreal, Quebec, Canada
[8]Maisonneuve-Rosemont Hospital, Montreal, Quebec, Canada
[9]McMaster University, Hamilton, Ontario, Canada
[10]Nanaimo Regional General Hospital, Nanaimo, British Columbia, Canada
[11]University of Alberta, Edmonton, Alberta, Canada
[12]JSS Medical Research Inc., St-Laurent, Quebec, Canada
[13]McGill University, Montreal, Quebec, Canada
[14]Janssen Inc. Medical Affairs, Toronto, Ontario, Canada

Contributors All authors satisfy the ICMJE authorship criteria, namely: Substantial contributions to the conception or design of the work (ER, FN, MS), or the acquisition (DS, WGB, MK, AC, MZ, SS, MS, SD, DS), analysis (EP, ER, JSS) or interpretation of data (DS, WGB, MK, AC, MZ, SS, MS, SD, DS, EP, JSS, VL, AJL, FN, ER, SO, MS). Drafting the work or revising it critically for important intellectual content (DS, WGB, MK, AC, MZ, SS, MS, SD, DS, EP, JSS, VL, AJL, FN, ER, SO, MS). Final approval of the version published (DS, WGB, MK, AC, MZ, SS, MS, SD, DS, EP, JSS, VL, AJL, FN, ER, SO, MS). Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (DS, WGB, MK, AC, MZ, SS, MS, SD, DS, EP, JSS, VL, AJL, FN, ER, SO, MS).

Funding Janssen Inc.

Competing interests PR has received grants and/or honoraria for his roles as investigator and/or consultant with: Janssen, Abbott, AbbVie, Amgen, BMS, Pfizer, Novartis and Merck. DC has received grants and/or honoraria for his roles as investigator and/or consultant with: Abbott, Amgen, AstraZeneca, BMS, Merck-Schering, Janssen, Lilly, Novartis, Pfizer and Wyeth, Roche, UCB. WGB has received grants and/or honoraria for his roles as investigator and/or consultant with: Abbvie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Novartis, Pfizer, Roche, Servier, UCB, Warner Chilcott. MK has received grants and/or honoraria for his roles as investigator and/or consultant with: Abbvie, Amgen, BMS, Janssen, Lilly, Pfizer, Roche, UCB. AC has received grants and/or honoraria for his roles as investigator and/or consultant with: Abbott, Amgen, BMS, Celgene, Merck-Schering, Janssen, Pfizer and Wyeth, Roche, UCB. MZ has received grants and/or honoraria for his roles as investigator and/or consultant with: Abbvie, Amgen, BMS, Celgene, GSK, JNJ, Lilly, Pfizer, UCB. SS has received grants and/or honoraria for his roles as investigator and/or consultant with: Abbott, Amgen, BMS, Merck-Schering, Janssen, Lilly, Novartis, Pfizer and Wyeth, Roche, UCB. MS has received grants and/or honoraria for his roles as investigator and/or consultant with: Abbvie, Janssen, Amgen, BMS, UCB. SD has received grants and/or honoraria for his roles as investigator and/or consultant with: Abbott, Amgen, AstraZeneca, BMS, Merck-Schering, Janssen, Lilly, Pfizer and Wyeth, Roche, Takeda, UCB. DS has received grants and/or honoraria for his roles as investigator and/or consultant with: Janssen, Abbvie, Pfizer, Amgen, Celgene, Roche, BMS. VL, AJL, FN, SO and MS are employees of Janssen Inc. EP, JSS and ER are employees of JSS Medical Research, the contract research organisation mandated to manage the study and conduct data analysis.

Patient consent Obtained.

Ethics approval Ethics committee/institutional review board approval was obtained from the respective Research Ethics Boards (REB) of participating institutional sites and a Central Institutional Review Board (IRB Services, Ontario Canada) for private practice sites.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002;346:1349–56.
2. Braun J. [Ankylosing spondylitis]. *MMW Fortschr Med* 2009;151:79–83.
3. Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002;136:896–907.
4. Sieper J, Braun J, Rudwaleit M, *et al*. Ankylosing spondylitis: an overview. *Ann Rheum Dis* 2002;61(Suppl 3):iii8–18.
5. The Arthritis Society. *Ankylosing spondylitis*. The Arthritis Society, 2013.
6. Boonen A, Severens JL. Ankylosing spondylitis: what is the cost to society, and can it be reduced? *Best Pract Res Clin Rheumatol* 2002;16:691–705.
7. Boonen A, van der HD, Landewe R, *et al*. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. *Ann Rheum Dis* 2003;62:732–40.
8. Kobelt G, Andlin-Sobocki P, Brophy S, *et al*. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). *Rheumatology (Oxford)* 2004;43:1158–66.
9. Ward MM. Functional disability predicts total costs in patients with ankylosing spondylitis. *Arthritis Rheum* 2002;46:223–31.
10. Boonen A. Socioeconomic consequences of ankylosing spondylitis. *Clin Exp Rheumatol* 2002;20:S23–6.
11. Mau W, Listing J, Huscher D, *et al*. Employment across chronic inflammatory rheumatic diseases and comparison with the general population. *J Rheumatol* 2005;32:721–8.
12. Barlow JH, Wright CC, Williams B, *et al*. Work disability among people with ankylosing spondylitis. *Arthritis Rheum* 2001;45:424–9.
13. Haroon N, Inman RD, Learch TJ, *et al*. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2013;65:2645–54.
14. Toussirot E, Wendling D. Current guidelines for the drug treatment of ankylosing spondylitis. *Drugs* 1998;56:225–40.

15. Rudwaleit M, Sieper J. Infliximab for the treatment of ankylosing spondylitis. *Expert Opin Biol Ther* 2005;5:1095–109.
16. Braun J, Landewe R, Hermann KG, *et al*. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. *Arthritis Rheum* 2006;54:1646–52.
17. Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care Res (Hoboken)* 2011;63(Suppl 11):S47–58.
18. Maksymowych WP, Jhangri GS, Lambert RG, *et al*. Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. *J Rheumatol* 2002;29:959–65.
19. Stone M, Salonen D, Lax M, *et al*. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. *J Rheumatol* 2001;28:1605–14.
20. Temekonidis TI, Alamanos Y, Nikas SN, *et al*. Infliximab therapy in patients with ankylosing spondylitis: an open label 12 month study. *Ann Rheum Dis* 2003;62:1218–20.
21. Van den Bosch F, Kruithof E, Baeten D, *et al* Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. *Ann Rheum Dis* 2000;59:428–33.
22. Braun J, Baraliakos X, Golder W, *et al*. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. *Arthritis Rheum* 2003;48:1126–36.
23. Rudwaleit M, Baraliakos X, Listing J, *et al*. Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. *Ann Rheum Dis* 2005;64:1305–10.
24. Vander Cruyssen B, Ribbens C, Boonen A, *et al*. The epidemiology of ankylosing spondylitis and the commencement of anti-TNF therapy in daily rheumatology practice. *Ann Rheum Dis* 2007;66:1072–7.
25. Collantes E, Zarco P, Munoz E, *et al*. Disease pattern of spondyloarthropathies in Spain: description of the first national registry (REGISPONSER) extended report. *Rheumatology (Oxford)* 2007;46:1309–15.
26. Dincer U, Cakar E, Kiralp MZ, *et al*. Diagnosis delay in patients with ankylosing spondylitis: possible reasons and proposals for new diagnostic criteria. *Clin Rheumatol* 2008;27:457–62.
27. Brandt HC, Spiller I, Song IH, *et al*. Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. *Ann Rheum Dis* 2007;66:1479–84.
28. Zink A, Thiele K, Huscher D, *et al*. Healthcare and burden of disease in psoriatic arthritis. A comparison with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol* 2006;33:86–90.
29. Deyo RA, Weinstein JN. Low back pain. *N Engl J Med* 2001;344:363–70.
30. Rudwaleit M, Listing J, Brandt J, *et al*. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:665–70.
31. Thorne C, Bensen WG, Choquette D, *et al*. Effectiveness and safety of infliximab in rheumatoid arthritis: analysis from a Canadian multicentre prospective observational registry. *Arthritis Care Res (Hoboken)* 2014;66:1142–51.
32. Pavelka K, Forejtova S, Stolfa J, *et al*. Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA. *Clin Exp Rheumatol* 2009;27:958–63.
33. Bodur H, Ataman S, Bugdayci DS, *et al*. Description of the registry of patients with ankylosing spondylitis in Turkey: TRASD-IP. *Rheumatol Int* 2012;32:169–76.
34. Glintborg B, Ostergaard M, Krogh NS, *et al*. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor alpha inhibitor therapy: results from the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2013;72:1149–55.
35. Brandt J, Haibel H, Cornely D, *et al*. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000;43:1346–52.
36. Haibel H, Song IH, Rudwaleit M, *et al*. Multicenter open-label study with infliximab in active ankylosing spondylitis over 28 weeks in daily practice. *Clin Exp Rheumatol* 2008;26:247–52.
37. van der Linden SM, Valkenburg HA, de Jongh BM, *et al*. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum* 1984;27:241–9.
38. Fabbroni M, Cantarini L, Caso F, *et al*. Drug retention rates and treatment discontinuation among anti-TNF-alpha agents in psoriatic arthritis and ankylosing spondylitis in clinical practice. *Mediators Inflamm* 2014;2014:862969.
39. Lie E, Kristensen LE, Forsblad-d'Elia H, *et al*. The effect of comedication with conventional synthetic disease modifying antirheumatic drugs on TNF inhibitor drug survival in patients with ankylosing spondylitis and undifferentiated spondyloarthritis: results from a nationwide prospective study. *Ann Rheum Dis* 2015;74:970–8.
40. Boonen A, van der Heijde D, Landewe R, *et al*. Costs of ankylosing spondylitis in three European countries: the patient's perspective. *Ann Rheum Dis* 2003;62:741–7.
41. Lee W, Reveille JD, Davis JC Jr, *et al*. Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. *Ann Rheum Dis* 2007;66:633–8.
42. Healey EL, Haywood KL, Jordan KP, *et al*. Impact of ankylosing spondylitis on work in patients across the UK. *Scand J Rheumatol* 2011;40:34–40.
43. Boonen A. A review of work-participation, cost-of-illness and cost-effectiveness studies in ankylosing spondylitis. *Nat Clin Pract Rheumatol* 2006;2:546–53.
44. Boonen A, van der HD, Landewe R, *et al*. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Ann Rheum Dis* 2002;61:429–37.
45. Kobelt G, Andlin-Sobocki P, Maksymowych WP. Costs and quality of life of patients with ankylosing spondylitis in Canada. *J Rheumatol* 2006;33:289–95.
46. Verstappen SM, Bijlsma JW, Verkleij H, *et al*. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. *Arthritis Rheum* 2004;51:488–97.
47. Braun J, Brandt J, Listing J, *et al*. Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. *Ann Rheum Dis* 2005;64:229–34.
48. van der Heijde D, Kivitz A, Schiff MH, *et al*. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006;54:2136–46.