Real-world evidence of TNF inhibition in axial spondyloarthritis: can we generalise the results from clinical trials?

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ABSTRACT

Management guidelines assume that results from clinical trials can be generalised, although seldom is data available to test this assumption. We aimed to determine the proportion of patients commencing TNF inhibition (TNFi) who would have been eligible for relevant clinical trials, and whether treatment response differs between these groups, and the trials themselves.

The British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS) recruited a real-world cohort of TNFi-naïve spondyloarthritis patients with data collection from clinical records and patient questionnaires. Participant characteristics were extracted from trials identified from a recent Health Technology Assessment of TNFi for ankylosing spondylitis / non-radiographic axial spondyloarthritis. Descriptive statistics were used to determine the differences, including treatment response, between BSRBR-AS participants who would/would not have been eligible for the clinical trials, and with trial participants.

Among 2420 BSRBR-AS participants, those commencing TNFi (34%) had shorter symptom duration (15 versus 22yrs) but more active disease (BASDAI 6.4 versus 4.0; BASFI 6.2 versus 3.8). Of those commencing TNFi, 41% met eligibility criteria for ≥1 of fourteen relevant trials; they reported higher disease activity (BASDAI 6.9 versus 6.1) and poorer function (BASFI 6.6 versus 6.0). 62% of trial participants reported a positive treatment response, versus 51% of BSRBR-AS patients (difference: 10%; 95%CI: 4 to 16%). Potential eligibility for trials did not influence treatment response (difference 2.0%; -9.4 to 13.4%).

Fewer patients in the real-world respond to TNFi than is reported in the trial literature. This has important implications for the generalisability of trial results, and the cost-effectiveness of TNFi agents.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic arthritis affecting the sacroiliac joints and spine, although peripheral joint involvement is common, as are several extra-articular features. Treatment, historically, has been with non-steroidal anti-inflammatory drugs, plus physiotherapy/hydrotherapy, although TNFα inhibitors (TNFi) have revolutionised patient management. Targeting inflammation and reducing disease activity,[1] they also have demonstrable effects on outcomes identified as important for patients, such as work productivity, [2] and their use is common: we have shown that, in the Scotland Registry for Ankylosing Spondylitis, around one-third of patients either are, or have been, on TNFi.[3]

In 2009 the Assessment of Spondyloarthritis International Society (ASAS) proposed the patients were classified according to whether they have imaging evidence of sacroiliitis; and if so, whether there are x-ray changes, or not.[4] In the UK, early guidelines from the British Society for Rheumatology (BSR),[5] and the National Institute of Health and Care Excellence (NICE),[6;7] advocated TNFi only among patients with radiological evidence of sacroiliitis – reflecting the patient population of trials at the time. More recent guidance recommends that in the absence of evidence of radiological sacroiliitis patients may be offered TNFi providing they have a positive MRI and/or elevated acute phase reactants.[8] Similarly, the updated NICE Technology Appraisal approves five agents for the treatment of ankylosing spondylitis, three of which may also be used for the treatment of non-radiographic axSpA.[9]

Much of what we know about the benefits of TNFi in axSpA comes from clinical trials, although it is acknowledged that patients recruited to trials may not be representative of the routine clinical population. Trials often have restrictive eligibility criteria and recruit patients from specialist centres. In rheumatoid arthritis it has been demonstrated that only a small proportion of patients in observational clinical cohorts meet biologic agent trial eligibility criteria, raising concern about the extrapolation of the trial results.[10] Others have provided some evidence that DMARD treatment response may be superior among randomised trial participants than in daily clinical practice, although the data was equivocal.[11] However, the assumption is commonly made that the treatment response observed in trials will be generalisable to the wider patient population – although seldom is data available to test this assumption.

The current study takes advantage of a large nationwide cohort providing real-world evidence on the use of biologics in axSpA and aims to determine the proportion of patients commencing TNFi in a real-world setting who may or may not have been eligible for the clinical trials that led to the licencing and approval of TNFi, and to determine whether there is a difference in treatment response between these groups.

METHODS

BSRBR-AS data

Between December 2012 and December 2017, the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS) recruited patients meeting the ASAS classification criteria for axSpA (4) who were naïve to biologic therapy. The protocol is published elsewhere,(12) but in brief: patients were recruited from 83 rheumatology departments across Great Britain. Initially, only patients meeting the ASAS imaging criteria were eligible, although from November 2014 patients meeting the ASAS clinical criteria were also included. Patients remaining on conventional therapy were recruited into a non-biologic cohort; whereas those commencing TNFi were recruited into a biologic cohort. Eligible biologic agents included Adalimumab (Humira) and Etanercept (Enbrel) from the start of study, plus Certolizumab Pegol (Cimzia) from August 2015, and Etanercept (Benepali) from November 2016. All patients were followed up annually, with additional follow-up at 3-months and 6-months for patients commencing TNFi.

Clinical data was collected from medical records, including: spinal mobility (Bath Ankylosing Spondylitis Metrology Index; BASMI (13)), acute phase reactants (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), and extra-articular features (uveitis, psoriasis, inflammatory bowel disease). Information was also collected on the use of other medication, and on various comorbidities (angina, congestive heart failure, stroke, hypertension, diabetes, asthma, bronchitis, peptic ulcer, liver disease, renal disease, tuberculosis, demyelination, depression and malignancy). At each point, participants were sent a postal questionnaires, asking about lifestyle factors, disease activity (Bath Ankylosing Spondylitis Disease Activity Index; BASDAI (14)) and function (Bath Ankylosing Spondylitis Disease Functional Index; BASFI (15)).

Randomised trial data

Placebo-controlled randomised controlled trials to determine the clinical effectiveness of the TNF inhibitors were identified from the Health Technology Assessment that informed the NICE Technology Appraisal on TNFi for ankylosing spondylitis and non-radiographic axial spondyloarthritis.(16) Key characteristics of trial participants were extracted from the original articles for the TNFi agents included in the BSRBR-AS, including, where available: age and gender, disease duration, disease activity (BASDAI), function (BASFI), spinal mobility (BASMI), HLA-B27 status, plus an objective measure of inflammation (CRP).

Detailed information on trial inclusion/exclusion criteria was extracted; including the age and disease state of included participants, plus diagnoses which would necessitate exclusion (see supplementary information; Table S1). For each participant in the BSRBR-AS commencing Humira, a count was made of how many Humira

trials that patient would have been eligible for. This was repeated for Cimzia, and Enbrel trials were used for patients starting either Enbrel or Benepali.

Statistical analysis

Simple descriptive statistics were used to describe the BSRBR-AS cohort and the differences between participants who were/were not commencing TNFi. Characteristics of trial participants were summarised by pooling data across trials using a weighted arithmetic mean. Differences between trial and BSRBR-AS participants were then quantified and presented with 95% confidence intervals. Treatment response was determined using the ASAS-20 response criteria, a four-domain outcome based on patient global assessment, pain, function and inflammation[17] and the most common outcome measure reported in the trials. For BSRBR-AS patients commencing TNFi, treatment response was determined at the first contact with the study in the period 10 weeks to 9 months after commencement of TNFi therapy. This permitted measurement of the outcome within the first two follow-up periods of the study (but allowing for early or late clinic visits).

All analysis was conducted in Stata 14.1 (StataCorp, College Station, Texas) and used the June 2017 version of the BSRBR-AS dataset.

Ethical approval

The study was approved by the National Research Ethics Service (NRES) Committee North East – County Durham and Tees Valley (Research Ethics Committee (REC) reference 11/NE/0374).

RESULTS

The 83 BSRBR-AS participants had a mean age of 48yrs (SD=14); 68% were male; and 67% met the modified New York criteria for ankylosing spondylitis, 29% met the ASAS axSpA imaging criteria but not the modified New York, and 4% met solely the ASAS clinical criteria. Mean age at symptom onset was 29yrs (SD=12) and mean symptom duration was 19yrs (SD=14) and at recruitment participants had a mean CRP of 43 (SD=216) mgL^{-1}. In clinic, 57% had been tested for HLA-B27, of whom 81% were positive. 816 participants (34%) were starting TNFi: 526 (64%) were starting Adalimumab (Humira); 207 (25%) Etanercept (Enbrel); 17 (2%) Etanercept (Benepali); and 66 (8%) Certolizumab Pegol (Cimzia). Median time from treatment decision to commencing therapy was 24 days (inter-quartile range (IQR): 0-46 days).

Participants commencing TNFi were younger (mean age 44.3 versus 50.1yrs; difference 5.8yrs (95%CI: 4.6, 7.0yrs)). They had shorter symptom duration (mean duration 14.9 versus 21.8yrs; difference 6.9yrs (5.7, 8.1yrs)) and more severe disease, as determined by the Bath Indices (mean BASDAI 6.4 versus 4.0; difference 2.4 (2.2, 2.6); mean BASFI 6.2 versus 3.8; difference 2.3 (2.1, 2.6); and mean BASMI 4.2 versus 3.6; difference 0.6 (0.4, 0.8)).

Randomised trial data

Fourteen randomised trials were identified, comprising 2437 participants, including six for Humira (N=1018), one for Cimzia (N=325) and seven for Enbrel (n=1094). Trial inclusion criteria were broadly similar, requiring active disease (commonly defined as a BASDAI ≥4 out of ten) plus a combination of back pain, morning stiffness and a failure to tolerate NSAIDs. Whereas, exclusion criteria mainly related to prior/current therapy or persons with a relevant history in relation to safety issues under investigation (see supplementary information; Table S1).

Trial participants had a mean age of 38yrs; 71% were male. Participants had a mean disease duration of 8.5yrs and mean disease activity (BASDAI), function (BASFI) and metrology (BASMI) indices of 6.2, 5.1 and 3.3 respectively. 82% were HLA-B27 positive and participants had a mean CRP of 17 mgL^{-1}.

There were several differences between the randomised trial participants and the BSRBR-AS biologic cohort (see Figure 1 and Table 1). Although the differences were not large, the BSRBR-AS had a significantly smaller proportion of male participants (67% versus 71%) and a lower proportion of participants who were HLA-B27 positive (76% versus 82%). BSRBR-AS participants were approximately 6yrs older than trial participants although no real difference in disease duration. They reported similar disease activity (BASDAI: 6.4 versus

6.2; difference 0.2; 95%CI -0.3, 0.7), although poorer function (BASFI: 6.2 versus 5.1; difference 1.1; 95%CI 0.5, 1.8) and poorer spinal mobility (BASMI: 4.2 versus 3.3; difference 1.0; 95%CI 0.8, 1.1).

Treatment response

Of the 816 BSRBR-AS participants commencing TNFi, only 333 (41%) would have been eligible for any of the relevant trials (see Table 2). There were differences between agents: Adalimumab (30%), Certolizumab Pegol (50%), and Etanercept (64%).

There were no large differences between BSRBR-AS biologic cohort participants who did/did not meet any clinical trial eligibility criteria (see Table 3). However, a slightly higher disease activity was reported among participants who would have been eligible for at least one trial, versus those eligible for none (BASDAI: 6.9 versus 6.1; difference 0.8; 95%CI 0.5, 1.1). Similarly, participants eligible for at least one trial reported poorer function (BASFI: 6.6 versus 6.0; difference 0.6; 95%CI 0.2, 1.0).

Ten of the fourteen trials reported ASAS20 response criteria, and 864/1401 participants reported a positive treatment response (61.7%). In the BSRBR-AS biologic cohort, follow-up data was available for 318 (39%), in whom 163 (51.3%) achieved an ASAS20 treatment response (difference: 10.4%; 95%CI: 4.4, 16.5%). Exactly 50% of participants who would have been eligible for at least one clinical trial achieved a positive treatment response, compared to 52% of those who did not meet any trial eligibility criteria (difference 2.0%; 95%CI: -9.4, 13.4%).

DISCUSSION

This is the first paper of which we are aware to examine the generalisability of results from trials to real-world prescribing in axSpA. We have shown that there are a number of differences in patients commencing TNFi, versus those in the trials that led to the licencing of these drugs. In clinical trials, participants are more likely to be male, younger and HLA-B27 positive. Also, despite similar disease activity , they are likely to report better function prior to treatment. Reassuringly, treatment response in BSRBR-AS biologic patients was unrelated to whether they would have met eligibility for the trials although, overall, treatment response was significantly lower than that reported in clinical trials.

It is important to consider what might explain these findings – especially because the likelihood of meeting response criteria was not related to factors determining eligibility for trials. BSRBR-AS participants were approximately 6yrs older and we have previously demonstrated that for every additional year of age, there is a 1% reduction in the odds of achieving ASAS20 treatment response. However, this difference is not statistically significant (odds ratio: 0.99 (95%CI: 0.97, 1.004))(18) and cannot explain the difference observed in the current study. Across several different response criteria this previous work has also shown that persons who do not respond to TNFi are characterised by not being in full-time employment, and by leaving formal education earlier; they report higher scores on questionnaires of mood and mental health, and experience fewer comorbidities.(18) With the exception of various specific comorbidities, none of these were trial exclusion criteria . It is possible that there is a selection of patients into trials favouring those who are better educated, with higher socioeconomic status, better mental and overall health. This would explain why treatment response in the BSRBR-AS was lower than that achieved in the trials, even though basic clinical characteristics between studies are broadly similar. Alternatively, and equally plausible, it may be that non-specific effects are stronger in randomised trials, with the overt experimental testing of a novel agent, and with intensive follow-up. This is speculative, although underlines the importance of harnessing these effects in the real world.

There is an argument that, due to classification criteria being misused for diagnostic purposes, a proportion of patients, in reality, do not have axSpA. It is possible, therefore, that if this occurs with greater frequency in the BSRBR-AS than in the trial populations, then this might contribute to the difference in treatment response between groups. However, 96% of the BSRBR-AS participants had objective evidence of sacroiliitis – the defining features of axSpA – and thus any effect of this in the current study is likely to be small.

Could the findings be explained by selective attrition? Although fewer BSRBR-AS participants provided follow-up data than in the clinical trials, to account for the observed difference BSRBR-AS participants lost to

follow-up would have to be one-third more likely to achieve ASAS20 response than those who provided follow-up data. We believe this is unlikely.

ASAS-20 is one of many available outcome measures. Indeed, recently, other trials have adopted a higher bar, such as ASAS-40. However, ASAS-20 was chosen for the pragmatic reason that, among the relevant trials it was the most common outcome measure (10 of 14 trials) and was therefore the most appropriate measure for comparison. Ideally, we could have examined a composite measure encapsulating patient-reported and objectively measured aspects, such as change in the Ankylosing Spondylitis Disease Activity Score (ASDAS). Pooling observational data from 12 registries across Europe, others have shown that nearly twice as many patients report ASAS-20 response at six-months, compared to the proportion who achieve ASDAS inactive disease: 64% versus 33%.(19) There were also differences in the timing of outcome measurement between the clinical trials and the BSRBR-AS. All trials measured treatment outcome at 12wks ; whereas, in the BSRBR-AS, treatment response was assessed at the first study contact between 10wks and 9months. This is a pragmatic reflection of clinical practice, where data collection is not mandated by study protocol. Could this explain the current findings? In the longer term, it may be that patients who achieve satisfactory treatment response are less likely to attend clinic (although infrequent attendance may result in cessation of treatment). However, it is harder to argue that this is likely for the first follow-up, when the initial treatment response (and maintenance of therapy) is to be determined.

The context of a randomised trial and routine clinical practice differ markedly. In trials, treatment is likely to commence soon after randomisation, and the identification of early treatment failure is important because of the ethical imperative to get participants randomised to placebo switched to the treatment that is believed to be superior. Whereas, in the real world, after the clinical decision has been made for a patient to start TNFi, it may take several weeks for a patient to receive the medication. The counter-argument is that, in the real-world, a physician may wish to start certain patients on active treatment immediately, rather than 'risk' randomisation to placebo. These patients, unlikely to be in the trial, may be less likely to achieve a good treatment response.

In the BSRBR-AS treatment response was determined at the first follow-up data point at least 10wks, but no more than 9months after commencing TNF inhibition. The median (IQR) follow-up was 14wks (12-7wks) and all participants, by definition, had been on therapy for at least 2.5months. Although the timing of outcome in the clinical trials was more consistent, at 12wks, it is unlikely that the superior treatment response in the trials is due to large differences in follow-up.

Finally, one must also consider the generalisability of findings to other TNFi agents. Patients in trials probably get better overall care: the follow-up response rate is certainly greater, and this emphasises the importance

of regular patient follow-up, perhaps even with treat-to-target strategies. Indeed, one may argue that this may be more important than which specific agent is administered. Although there are other anti-TNF agents (and indeed non-anti-TNF biologics), we only included clinical trials reporting Adalimumab (Humira), Certolizumab Pegol (Cimzia) and Etanercept (Enbrel and Benepali). This omission was important to preserve comparability between the trial data and the BSRBR-AS in which patients commencing other agents were not eligible for recruitment. It would be interesting to replicate this analysis with other agents, including recent biosimilars, although it is hard to think of why the similarities and differences between real-world and trial data would be different to the results that are reported here.

In summary, using a large nationally representative sample of patients with axSpA, we have shown several differences between patients commencing TNFi and the trial populations that led to the treatment guidelines – and, ultimately, access to – these agents. Participants in clinical trials tend to have better function and spinal mobility, and lower CRP prior to the commencement of therapy. However, we found no difference in disease activity, the key feature indicating commencement of TNFi.

While the rheumatologist will already exercise caution when generalising trial results to the patients in clinic – and we provide evidence in support of this – the development of clinical guidelines is based on data from randomised trials. We have shown that in the real world, the proportion of patients who achieve a satisfactory treatment response is lower than is observed in the trials themselves. The inferior treatment response in patients outside the trial setting has important implications for the cost-effectiveness of these agents, particularly with incremental cost effectiveness ratios approaching thresholds that are considered acceptable (16). In the era of biosimilars the cost-effectiveness of originator products is already being challenged.

Patients with an increasing number of comorbidities are likely to be excluded from clinical trials. We have shown elsewhere that this is also a predictor of response to TNFi in a real-world spondyloarthritis population.(18) In addition, we found that higher socioeconomic status, longer education and better mental health were independent predictors of response. We hypothesise that there is a selection bias into randomised clinical trials favouring the more educated and more affluent, and those with better mental health, and that this results in trial participants having a superior chance of positive outcome, compared to the real-world patients that they ostensibly represent.

KEY MESSAGES

- What is already known about this subject?

Data on the benefits of TNF inhibition come from clinical trials, although trial populations are seldom representative of the routine clinic population. It is unclear, therefore, how generalisable the data actually is.

- What does this study add?

Fewer patients in the real-world respond to TNFi than is reported in the trial literature. This has important implications for the generalisability of trial results, and the cost-effectiveness of TNFi agents. Treatment response is unrelated to whether patients would have met eligibility for clinical trials although, overall, it is than in trials populations.

- How might this impact on clinical practice?

The rheumatologist needs to consider that the proportion of patients who achieve a satisfactory treatment response to TNF inhibition will be lower than might be expected from clinical trials. This has implications for cost-effectiveness of therapy and perhaps, therefore, choice of agent.

CONTRIBUTORSHIP

GTJ and GJM designed the study and oversaw data collection (primary data). LED extracted the data (literature review). GTJ conducted the analysis and all authors were involved in interpretation of data. GTJ drafted the manuscript to which all authors provided critical contribution. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors have given final approval of the version to be submitted for publication and agree 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.

COMPETING INTERESTS

The authors have no relevant interests to declare.

PATIENT AND PUBLIC INVOLVEMENT

The British Society for Rheumatology's Registers Committee, which oversees the running of the BSRBR-AS has patient representation from several arthritis charities, including the (UK) National Axial Spondyloarthritis Society. Although no patients or public were involved in the analysis for this manuscript, the research question was identified at a priority setting exercise involving scientists, rheumatology consultants, and patient representatives.

DATA SHARING

Data from the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis is available to external investigators, on reasonable request. For information on how to access data, see: www.rheumatology.org.uk.

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FIGURES AND TABLES

Figure 1   *Differences between BSRBR-AS biologic cohort and randomised trial participants*

(See separate file.)

Table 1   Key characteristics of BSRBR-AS biologic cohort, versus randomised trial participants

		BSRBR-AS[1]		Randomised trials[1]		Difference[2] (95%CI)	
Sex (male)		67.2%	(n=816)	71.3%	(n=2437)	-4.1%	(-7.8%, -0.4%)
Mean age (years)		44.3	(n=816)	37.9	(n=2114)	6.4	(5.4, 7.3)
Disease duration (years)		8.1	(n=816)	8.5	(n=1534)	-0.4	(-1.1, 0.4)
Bath indices[3]	Mean BASDAI	6.4	(n=699)	6.2	(n=2036)	0.2	(-0.3, 0.7)
	Mean BASFI	6.2	(n=707)	5.1	(n=2076)	1.1	(0.5, 1.8)
	Mean BASMI	4.2	(n=604)	3.3	(n=1512)	1.0	(0.8, 1.1)
CRP (mgL^{-1})		43.3	(n=699)	16.7	(n=1644)	26.6	(16.1, 37.1)
HLA-B27 positive		75.7%	(n=543)	82.3%	(n=1939)	-6.6%	(-10.6%, -2.6%)

1   Numbers vary for BSRBR-AS, due to missing data. Numbers vary for randomised trials because not each trial reported each characteristic.
2   BSRBR-AS minus trials. Therefore, a positive result indicates a higher value in the BSRBR-AS biologic cohort.
3   BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index

Table 2   Count of trials for which BSRBR-AS participants met eligibility criteria

N (trials)	Adalimumab (6 trials)				Etanercept (7 trials)				Certolizumab pegol (1 trial)			
	N	%	Trials	Cumv %[1]	N	%	Trials	Cumv %[1]	N	%	Trials	Cumv %[1]
0	370	70.3%	–	–	80	35.7%	–	–	33	50.0%	–	–
1	42	8.0%	≥1	30%	39	17.4%	≥1	64%	33	50.0%	1[2]	50.0%
2	78	14.8%	≥2	22%	23	10.3%	≥2	47%				
3	7	1.3%	≥3	7%	14	6.3%	≥3	37%				
4	29	5.5%	≥4	6%	33	14.7%	≥4	30%				
5	0	0%	≥5	0%	35	15.6%	≥5	16%				
6	0	0%	6[2]	0%	0	0%	≥6	0%				
7					0	0%	7[2]	0%				

1   Cumulative percent – i.e. proportion of patients who meet eligibility criteria for at least this number of trials.
2   Maximum number of trials available, for this agent.

Table 3   Comparison of BSRBR-AS biologic cohort participants, those who did/did not meet any clinical trial eligibility criteria

		Eligible for any clinical trials	Not eligible for any clinical trials	Difference[1] (95%CI)	
Sex (male)		68.8%	66.0%	-2.7%	(-3.8%, 9.3%)
Mean age (years)		43.0	45.2	-2.2	(-4.0, -0.3)
Disease duration (years)		7.1	8.5	-1.7	(-3.2, -0.3)
Bath indices[2]	Mean BASDAI	6.9	6.1	0.8	(0.5, 1.1)
	Mean BASFI	6.6	6.0	0.6	(0.2, 1.0)
	Mean BASMI	4.2	4.3	-0.03	(-0.3, 0.3)
CRP (mgL^{-1})		34.8	49.2	-1.4	(-4.7, 1.8)
HLA-B27 positive		72.9%	77.5%	-4.6	(-12.1%, 2.9%)
ASAS20 treatment response		50.0%	52.0%	2.0%	(-9.4%, 13.4%)

1   Eligible minus non-eligible. Therefore, a positive result indicates a higher value in the 'eligible' sub-cohort.
2   BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index