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Authors

- Dr Thomas Williams; Great Western Hospitals NHS Foundation Trust (Rheumatology Department), Swindon, UK; (Corresponding and Lead Author- Thomas.williams5@nhs.net)
- Prof Alison Wadeley; Bath Spa University (College of Liberal Arts), Bath, UK;
- Ms Deborah Bond; Royal National Hospital for Rheumatic Diseases (Rheumatology Department), Bath, UK;
- Ms Charlotte Cavill; Royal National Hospital for Rheumatic Diseases (Research Department), Bath, UK;
- Ms Mandy Freeth; Royal National Hospital for Rheumatic Diseases (Research Department), Bath, UK;
- Dr Raj Sengupta; Royal National Hospital for Rheumatic Diseases (Rheumatology Department), Bath, UK;

Title

Real world experience of secukinumab treatment for ankylosing spondylitis at the Royal National Hospital for Rheumatic Diseases, Bath.

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Ethics

All data reported in this article was obtained from routine clinical practice. Patients included have all provided informed consent to enter the BathSpa biobank database for the purpose of research studies.

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Key points

1. Secukinumab was efficacious for improving short-term mean disease activity and function in our cohort of ankylosing spondylitis patients, regardless of whether used as the first, second, or third line biologic disease-modifying drug.
2. There were very low rates of discontinuation due to side effects in our cohort of secukinumab-treated ankylosing spondylitis patients.

Abstract

We reviewed our experience of treating ankylosing spondylitis patients with the IL-17 inhibitor secukinumab at the Royal National Hospital for Rheumatic Diseases, Bath. 76 patients were included, of whom secukinumab was the first line biologic drug used in 24, second line in 23 and third line in 29 patients, respectively. Only 5 patients discontinued the drug due to side effects before their first outpatient review, including 1 new case of inflammatory bowel disease. Significant improvements were seen in all disease outcome measures in patients receiving secukinumab as their first-line biologic agent, with a trend to improved mean BASDAI and BASFI even in patients receiving it as a second- or third-line biologic agent. This real world analysis adds to the evidence recommending secukinumab as a largely safe and effective treatment for ankylosing spondylitis.

Introduction/ objectives

Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting the spine, sacro-iliac and peripheral joints. Associated extra-articular manifestations include acute anterior uveitis, psoriasis and inflammatory bowel disease. There is increasing evidence that persistent spinal inflammatory disease may lead to increased new bone formation and damage in AS [1, 2].

The phase III MEASURE I study demonstrated the efficacy of secukinumab, a fully humanised monoclonal antibody against IL-17A, in reducing disease activity and improving AS symptoms in a clinical trial setting [3]. The National Institute for Health and Care Excellence (NICE) recommended secukinumab for the treatment of AS which is refractory to conventional therapy in 2016 [4].

The aim of our study is to retrospectively evaluate the efficacy and safety of secukinumab treatment in a real world cohort of AS patients, treated at the Royal National Hospital for Rheumatic Diseases (RNHRD) in Bath, United Kingdom.

Methods

Study design and patients

We performed a single-centre retrospective analysis in all AS patients treated with secukinumab at RNHRD who consented to inclusion in the BathSpA biobank. Data was obtained from outpatient clinic appointments as part of routine clinical practice. No additional data gathering was performed for the purpose of this study. There were no exclusion criteria.

Procedures and end points

In order to assess the efficacy of secukinumab, outcome measures were obtained at baseline and first follow-up assessment. We aimed for first follow-up after 16 weeks of treatment, however this duration varied between patients, reflecting our real world

experience. Outcome measures included Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life score (ASQOL), the Functional Assessment of Chronic Illness Therapy score (FACIT), EQ5D visual analogue score (EQ5D-VAS), and Jenkins Sleep Evaluation Questionnaire (JSEQ). We reported the absolute difference in mean outcome measures between baseline and first follow-up assessment after treatment (aiming for 16 weeks). As per NICE guidelines [4], secukinumab was deemed ineffective and discontinued if the patient failed to achieve an improvement by 2 points (or 50%) in both the BASDAI and spinal pain visual analogue score at this assessment.
In order to assess the safety of secukinumab, we have reported all patients who discontinued during longitudinal follow-up and the reason for discontinuation.

Statistical analysis
A T-test was used to calculate the two-tailed significance of the absolute mean difference in outcome measures following treatment, from which 95% confidence intervals were calculated. Mean differences with p-values less than 0.05 and 0.01 respectively were regarded as statistically significant. A sub-group analysis was subsequently performed to identify differences between patients who received secukinumab as the first, second or third line biologic disease modifying drug (bDMARD) for AS.

Results

Patients
76 patients (52 male, 24 female) were included. The age at diagnosis ranged from 19 to 42 years (mean age 27.3 years), with a mean disease duration of 25.3 years prior to starting secukinumab (range 0.8 to 41.0 years). The mean (and range of lowest; highest) baseline scores were as follows: BASDAI 6.7 (1.2; 9.0), BASFI 6.5 (1.0; 10.0), ASQOL 10.2 (2.0; 18.0), BASMI 3.2 (0.4; 7.4). Secukinumab was the first line bDMARD in 24 patients (17 male, 7 female), second line bDMARD in 24 patients (17 male, 7 female) and third line bDMARD in 28 patients (18 male, 10 female). bDMARDs prescribed prior to secukinumab are summarised in table 1 for patients receiving secukinumab second-line (part a) and third-line (part b).

Table 1: Summary of previous bDMARDs received by patients prior to initiation of secukinumab.

a) Secukinumab received as second-line bDMARD (n=24):

1st bDMARD	Number	%
Adalimumab	10	41.7
Etanercept	6	25.0
Etanercept (biosimilar)	2	8.3
Golimumab	3	12.5
Certolizumab pegol	2	8.3
Infliximab (biosimilar)	1	4.2

b) Secukinumab received as third-line bDMARD (n=28):

1st bDMARD	Number	%	2nd bDMARD	Number	%
Adalimumab	11	39.3	Adalimumab	13	46.4
Etanercept	10	35.7	Etanercept	9	32.1
Etanercept (biosimilar)	1	3.6	Etanercept (biosimilar)	2	7.1
Golimumab	2	7.1	Golimumab	1	3.6
Certolizumab pegol	2	7.1	Certolizumab pegol	2	7.1
Infliximab	1	3.6	Ustekinumab	1	3.6
Tocilizumab	1	3.6			

The mean delay between the baseline and first follow-up assessment of AS outcome measures was 25 weeks.

Clinical efficacy

The primary measures of clinical efficacy are summarised in table 2; parts a, b and c. Overall, the treatment efficacy of secukinumab was greater when given as a first line bDMARD, where significant improvements in all outcome measures were demonstrated. Nonetheless, secukinumab resulted in significant improvements in mean BASDAI when given as a second line bDMARD and mean BASFI when given as a third line bDMARD.

Table 2: Efficacy outcomes for patients receiving secukinumab for AS demonstrated by mean difference between baseline and first follow-up review. 'Significant differences: * p <.05; ** p < .01.
Abbreviations included are BASDAI: Bath Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life score; FACIT: Functional Assessment of Chronic Illness Therapy score; EQ5D-VAS: EQ5D visual analogue score; JSEQ: Jenkins Sleep Evaluation Questionnaire.

a: efficacy outcomes for patients receiving secukinumab as 1st line bDMARD (n=24).

Outcome measure	Baseline mean	Follow-up mean	Mean difference	95% confidence interval of difference	p-value of difference (2-tailed)
BASDAI	6.58	4.21	2.37 (36%)	0.73; 4.01	0.008**
BASFI	6.91	4.84	2.07 (30%)	0.64; 3.49	0.009**
ASQoL	12.56	7.00	5.56 (44%)	0.83; 10.28	0.027*
FACIT	21.63	32.38	-10.75 (-50%)	-23.15; 1.65	0.079
EQ5D-VAS	43.64	68.64	-25.00 (-57%)	-47.38; -2.62	0.032*
JSEQ	13.20	8.00	5.20 (39%)	0.62; 9.78	0.030*

b: efficacy outcomes for patients receiving secukinumab as 2nd line bDMARD (n=24).

Outcome measure	Baseline mean	Follow-up mean	Mean difference	95% confidence interval of difference	p-value of difference (2-tailed)
BASDAI	6.61	4.67	1.94 (29%)	0.68; 3.21	0.006**
BASFI	5.75	5.09	0.66 (11%)	-0.31; 1.63	0.164
ASQoL	12.73	11.60	1.13 (9%)	-3.66; 5.91	0.595
FACIT	21.60	22.00	-0.40 (-2%)	-6.33; 5.53	0.861
EQ5D-VAS	53.00	49.17	3.83 (7%)	-4.70; 12.37	0.301
JSEQ	13.22	10.22	3.00 (23%)	-0.94; 6.94	0.117

c: efficacy outcomes for patients receiving secukinumab as 3rd line bDMARD (n=28).

Outcome measure	Baseline mean	Follow-up mean	Mean difference	95% confidence interval of difference	p-value of difference (2-tailed)
BASDAI	5.66	4.89	0.77 (14%)	-0.20; 1.74	0.114
BASFI	5.85	5.02	0.83 (14%)	0.06; 1.61	0.036*
ASQoL	10.78	11.27	-0.49 (-5%)	-2.71; 1.73	0.644
FACIT	23.21	26.21	-3.00 (-13%)	-10.59; 4.59	0.409
EQ5D-VAS	54.58	52.92	1.67 (3%)	-11.00; 14.33	0.777
JSEQ	12.39	12.78	-0.39 (-3%)	-3.03; 2.25	0.760

In total, 16 patients discontinued treatment due to inefficacy. Of these, 4/24 (16.7%) were receiving secukinumab as the first line bDMARD, 6/24 (25%) were second line and 6/28 (21.4%) were third line. The previous bDMARDs used in the second and third line secukinumab non-responders and reasons for discontinuation of those drugs for each patient are listed in Table 3, parts a and b.

Table 3: Summary of previous bDMARDs received by secukinumab non-responders and primary reason for discontinuation of those drugs:

a) Secukinumab as second-line bDMARD (n=6):

Patient	1st line bDMARD	Reason for discontunation
1	Etanercept	Family planning
2	Golimumab	Side effects
3	Etanercept	Inefficacy
4	Etanercept	Inefficacy
5	Adalimumab	Inefficacy
6	Adalimumab	Inefficacy

b) Secukinumab as third-line bDMARD (n=6):

Patient	1st line bDMARD	Reason for discontunation	2nd line bDMARD	Reason for discontunation
1	Etanercept	Inefficacy	Adalimumab	Inefficacy
2	Golimumab	Side effects	Adalimumab	Inefficacy
3	Etanercept	Inefficacy	Adalimumab	Recurrent infections
4	Adalimumab	Recurrent infections	Etanercept	Inefficacy
5	Etanercept	Inefficacy	Adalimumab	Inefficacy
6	Etanercept	Inefficacy	Certolizumab pegol	Inefficacy

Safety

Of the 76 patients receiving secukinumab, 5 (6.6%) discontinued due to side effects. These include 1 de novo case of Crohn's disease, along with one case each of vertigo, low mood, mouth ulceration and sensory disturbance.

Discussion

Our real world experience of treating AS patients with secukinumab demonstrates a clear trend towards improved mean BASDAI and BASFI scores after six months' treatment, regardless of whether it is used as a first, second or third line bDMARD. 21.1% of patients discontinued secukinumab at the follow-up assessment due to inefficacy as defined by NICE guidelines (16.7% in bDMARD naïve versus 23.5% in previous bDMARD-treated patients). Although not a like-for-like comparison of efficacy, this contrasts with the 39% of secukinumab-treated patients who failed to achieve 20% improvement as per Assessment of SpondyloArthritis international Society criteria (ASAS20 response) after 16 weeks in the MEASURE I study [3]. Relatively few patients discontinued secukinumab due to adverse effects, although we did experience one newly diagnosed case of inflammatory bowel disease. Further work could include prospective analysis and head-to-head comparisons with other bDMARDs.

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