Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial

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Summary

Background **Ankylosing spondylitis is a chronic immune-mediated inflammatory disease characterised by spinal inflammation, progressive spinal rigidity, and peripheral arthritis. Interleukin 17 (IL-17) is thought to be a key inflammatory cytokine in the development of ankylosing spondylitis, the prototypical form of spondyloarthritis. We assessed the efficacy and safety of the anti-IL-17A monoclonal antibody secukinumab in treating patients with active ankylosing spondylitis.**

Methods **We did a randomised double-blind proof-of-concept study at eight centres in Europe (four in Germany, two in the Netherlands, and two in the UK). Patients aged 18–65 years were randomly assigned (in a 4:1 ratio) to either intravenous secukinumab (2×10 mg/kg) or placebo, given 3 weeks apart. Randomisation was done with a computer-generated block randomisation list without a stratification process. The primary efficacy endpoint was the percentage of patients with a 20% response according to the Assessment of SpondyloArthritis international Society criteria for improvement (ASAS20) at week 6 (Bayesian analysis). Safety was assessed up to week 28. This study is registered with ClinicalTrials.gov, number NCT00809159.**

Findings **37 patients with moderate-to-severe ankylosing spondylitis were screened, and 30 were randomly assigned to receive either intravenous secukinumab (n=24) or placebo (n=6). The final efficacy analysis included 23 patients receiving secukinumab and six patients receiving placebo, and the safety analysis included all 30 patients. At week 6, ASAS20 response estimates were 59% on secukinumab versus 24% on placebo (99·8% probability that secukinumab is superior to placebo). One serious adverse event (subcutaneous abscess caused by *Staphylococcus aureus*) occurred in the secukinumab-treated group.**

Interpretation **Secukinumab rapidly reduced clinical or biological signs of active ankylosing spondylitis and was well tolerated. It is the first targeted therapy that we know of that is an alternative to tumour necrosis factor inhibition to reach its primary endpoint in a phase 2 trial.**

Funding **Novartis.**

Introduction

Ankylosing spondylitis is a chronic immune-mediated inflammatory disease, with an estimated prevalence of 0·2–0·5% worldwide. It is characterised by spinal inflammation, progressive spinal ankylosis due to new bone formation, peripheral arthritis and enthesitis, extra-articular manifestations, familial clustering, and a strong genetic association with human leucocyte antigen (HLA)-B27.[1] Early onset of the disease in young adults, chronic spinal and extraspinal inflammation, and progressive irreversible structural damage can lead to important morbidity, functional deterioration, and socio-economic burden.

Non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy are the cornerstones of treatment for ankylosing spondylitis. Conventional disease-modifying anti-rheumatic drugs (DMARDs) are not effective for the axial symptoms of the disease. For patients with inadequate response to NSAIDs, treatment with tumour necrosis factor (TNF)-blockers has been recommended.[2] However, no approved alternative therapies are available for the roughly 40% of patients who do not tolerate or respond to TNF-blockers. Thus, there is an unmet need for medicines with new modes of action.

Interleukin 17A (IL-17A) has emerged as a novel therapeutic target for ankylosing spondylitis. First, the disease shows a strong genetic association with a series of protective polymorphisms in the IL-23 receptor (*IL23R*) gene, including rs11209026 (Arg381Gln).[3] Functional analyses have indicated that the Arg381Gln polymorphism impairs IL-23–dependent IL-17 production by Th17 cells, suggesting that genetically determined down-modulation of the IL-23/IL-17 axis could provide protection against ankylosing spondylitis.[4] Second, intracellular HLA-B27 misfolding leads to an unfolded protein response that potentiates abnormal IL-23 production,[5] and ankylosing spondylitis macrophages produce increased levels of IL-23.[6] Third, the number of

Published **Online** September 13, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61134-4

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(13)61913-3

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circulating CD4+IL-17+ cells is expanded in ankylosing spondylitis;[7] this includes KIR3DL2-expressing T cells that respond to cell-surface HLA-B27 homodimers[8] and IL-17–producing γ/δ T cells.[9] Fourth, inflamed target tissues indicate an ankylosing spondylitis-specific increase in IL-17–producing innate immune cells.[10,11] Fifth, spondyloarthritis in HLA-B27 transgenic rats and experimental ankylosing enthesitis in (BXSB×NZB) F1 mice were associated with an expansion of Th17 cells and with up-regulated IL-17 expression, respectively.[12] Moreover, IL-23 overexpression induces a spondyloarthritis-like disease in B10.RIII mice via RAR-related orphan receptor γt(+)CD3(+)CD4(–)CD8(–) T cells that produce IL-17 and IL-22.[13] Finally, trials with anti-IL-12/IL-23 and anti-IL-17 agents have shown significant clinical efficacy in psoriasis, a disease closely related to ankylosing spondylitis.[14–19]

We therefore undertook a proof-of-concept study to assess the efficacy and safety of secukinumab, a fully human anti-IL-17A monoclonal antibody, in patients with active ankylosing spondylitis.

Methods

Study design

We did a 28-week multicentre, randomised, double-blind, placebo-controlled study between March, 2009, and May, 2011, at eight centres in Europe (four in Germany, two in the Netherlands, and two in the UK; appendix). After a 4-week screening period, patients were randomly assigned (in a 4:1 ratio) to receive secukinumab or placebo at days 1 and 22.

See Online for appendix

The randomisation plan was generated by Novartis Drug Supply Management using a validated system. It was reviewed and approved by the Biostatistics Quality Assurance group of Novartis and locked after approval.

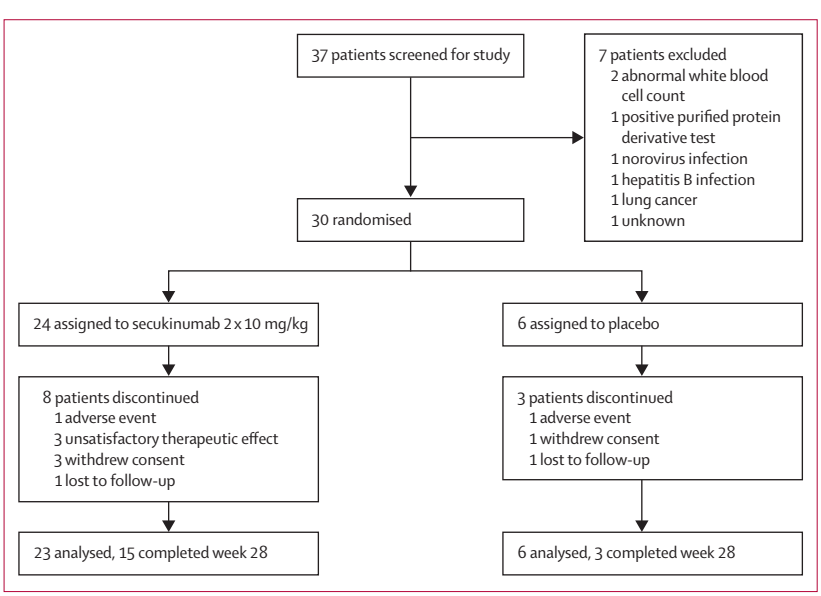

Figure 1: **Trial profile**

Randomisation was done by using a computer-generated block randomisation list without a stratification process. Data were accessible only to authorised personnel until database lock. The unblinded pharmacist or designated person (eg, study nurse) at each site received treatment allocation cards. When an eligible patient at a participating study site was to be entered into the study, the unblinded pharmacist or designated person completed a randomisation request by email to Novartis. The assigned randomisation number was returned to the pharmacist within 24 h of the request. After inclusion of each new patient, the pharmacist returned the email to confirm the patient's randomisation number and the date the patient received the first administration of study medication.

Efficacy and safety assessments were done up to week 28, with week 6 being the primary endpoint. All week-6 analyses were designated as interim analyses. All centres received approval from independent ethics committees or institutional review boards, and the study was done in accordance with the principles of the Declaration of Helsinki. Signed informed consent for the main and pharmacogenetic studies was obtained from each patient before any study-related procedures were undertaken. The full study protocol is available from the sponsor.

Patients

The study included 30 patients, 18–65 years of age, with definite ankylosing spondylitis as defined by the modified New York criteria,[20] a score of at least 4 on the Bath ankylosing spondylitis disease activity index (BASDAI), and a total back pain and nocturnal pain score of 40 or more on the visual analogue scale (0–100 mm), irrespective of the maximum tolerated doses of NSAIDs.

Major exclusion criteria included total spinal ankylosis, concomitant fulfilment of criteria for psoriatic arthritis, and presence of severe acute or subacute anterior uveitis. Patients with a history of or current stable psoriasis or inflammatory bowel disease were allowed to participate. Patients with active tuberculosis, hepatitis B or C, HIV, or any active systemic infection within the 2 weeks before baseline were excluded. Patients with latent tuberculosis had to complete their treatment and be considered cured before study entry. Patients with a history of malignancy (except basal cell carcinoma or adequately treated carcinoma in situ of the cervix) or significant cardiac, renal, neurological, psychiatric, endocrinologic, metabolic, or hepatic disease were also excluded.

Previous use of DMARDs, cyclosporine, azathioprine, or TNF-blockers was allowed. However, a maximum of ten patients with previous TNF-blocking therapy were allowed, to account for the possibility that response rates for secukinumab in such patients could be lower, thereby biasing the mean efficacy readout. Washout periods of 3 months for adalimumab and certolizumab and 2 months for etanercept and infliximab were required before baseline. Patients were allowed to continue any of

the following medications if the dosage remained stable for at least 4 weeks before the baseline visit and during the study: sulfasalazine (up to 3 g a day), methotrexate (up to 25 mg a week), prednisone or prednisone equivalent (up to 10 mg a day), and NSAIDs.

Study medication and dosage

The intravenous secukinumab dose of 10 mg/kg was based on previous pharmacokinetic and pharmacodynamic experience with secukinumab in rheumatoid arthritis.[15] A treatment regimen of two infusions of 10 mg/kg given intravenously 3 weeks apart was used to achieve high systemic exposure for induction of response, and because the 4-week toxicology coverage available at study start did not allow a longer treatment period.

Endpoints

The primary efficacy endpoint was the percentage of patients with a 20% response according to the Assessment of SpondyloArthritis international Society criteria for improvement (ASAS20) at week 6.[21] Secondary efficacy endpoints included ASAS40 (40% response according to ASAS criteria for improvement) and ASAS5/6 responses (improvement in five of six domains: pain, patient global assessment, function, inflammation, spinal mobility, C-reactive protein [acute-phase reactant] without deterioration in the 6th domain), BASDAI,[22] and assessment with the ankylosing spondylitis quality-of-life (ASQoL) measure.[23] All of these assessments were done at screening, baseline, days 8, 15, and 29, and weeks 6, 8, 10, 12, 16, 20, 24, and 28.

Biological endpoints, which were measured in secukinumab-treated patients, included erythrocyte sedimentation rate and serum C-reactive protein (CRP). Additionally, analyses of S100-proteins A8, A9, and A12 in secukinumab patients were done by multiplexed liquid chromatography–mass spectrometry multiple reaction monitoring. Sagittal MRI of the entire spine in secukinumab-treated and placebo-treated patients was done using short tau inversion recovery and T_1-weighted sequencing to assess bone marrow oedema at baseline, week 6, and week 28. MRI studies were analysed by an independent reader, who was blinded to treatment allocation and chronology of images, using the Berlin score.[24] To further assess the relevance of targeting IL-17A, 13 genetic polymorphisms that are either associated with ankylosing spondylitis or directly related to IL-17 were tested for association with response to secukinumab[25–27] (appendix). All genotyping was done by Novartis: single-nucleotide polymorphism (SNP) using TaqMan, and HLA genotyping using sequence-specific oligonucleotide probes. *ERAP1* transcript levels in whole blood were determined using Affymetrix DNA microarrays (Santa Clara, CA, USA).

Adverse events and vital signs were assessed at every visit for safety evaluations. Laboratory measurements were done at screening; baseline; days 2, 8, 15, 23, and 29; and weeks 6, 8, 10, 12, 16, 20, 24, and 28. Randomisation and blinding details are provided in the appendix.

Statistical analysis

The primary endpoint was analysed using Bayesian methods, as described previously.[28] For the placebo ASAS20 response rate, data from eight previous trials of ankylosing spondylitis (N=533) were included.[29] The information contained in these trials was transformed

	Secukinumab* (N=24)	Placebo (N=6)	Total (N=30)
Safety analysis dataset			
Age (years)	41·1 (10·10)	45·0 (9·96)	41·9 (10·03)
Men	14 (58%)	5 (83%)	19 (63%)
Race			
White	20 (83%)	6 (100%)	26 (87%)
Black	1 (4%)	..	1 (3%)
Asian	1 (4%)	..	1 (3%)
Other	2 (8%)	..	2 (7%)
Height (cm)	170·6 (8·00)	178·3 (3·50)	172·2 (7·92)
Weight (kg)	78·9 (15·52)	80·2 (14·80)	79·2 (15·14)
Body-mass index	27·1 (4·81)	25·3 (5·07)	26·7 (4·83)
Efficacy analysis dataset†			
Disease duration (years)	10·1 (12·20)	10·2 (12·02)	10·1 (11·95)
HLA-B27	16 (70%)	5 (83%)	21 (72%)
History of extra-axial involvement			
Uveitis	7 (30%)	2 (33%)	9 (31%)
Psoriasis	3 (13%)	1 (17%)	4 (14%)
Inflammatory bowel disease	3 (13%)	1 (17%)	4 (14%)
Dactylitis	1 (4%)	1 (17%)	2 (7%)
Peripheral arthritis	12 (52%)	4 (67%)	16 (55%)
Concomitant DMARD	8 (35%)	3 (50%)	11 (38%)
Methotrexate	4 (17%)	..	4 (14%)
Leflunomide	1 (4%)	..	1 (3%)
Sulfasalazine	5 (22%)	3 (50%)	8 (28%)
Other immunosuppressant‡	2 (9%)	..	2 (7%)
NSAID	22 (96%)	6 (100%)	28 (97%)
Steroid	3 (13%)	..	3 (10%)
Oral	2 (9%)	..	2 (7%)
Topical	1 (4%)	..	1 (3%)
Prior TNF-blocker	10 (43%)	3 (50%)	13 (45%)
ASQoL	12·1 (3·07)	10·3 (0·57)	11·7 (3·72)
BASDAI	7·1 (1·40)	7·2 (1·76)	7·1 (1·45)
BASMI	4·3 (1·86)	3·7 (1·11)	4·2 (1·73)
BASFI	6·4 (1·83)	5·3 (3·27)	6·2 (2·18)
MASES	4·3 (3·54)	1·7 (1·63)	3·8 (3·40)
LEI	1·2 (1·67)	0·2 (0·41)	1·0 (1·55)
CRP (mg/L)	13·3 (17·23)	13·2 (15·72)	13·3 (16·65)

Data are n (%) or mean (SD). DMARD=disease-modifying anti-rheumatic drug. NSAID=non-steroidal anti-inflammatory drug. TNF=tumour necrosis factor. ASQoL=ankylosing spondylitis quality-of-life. BASDAI=Bath ankylosing spondylitis disease activity index. BASMI=Bath ankylosing spondylitis metrology index. BASFI=Bath ankylosing spondylitis functional index. MASES=Maastricht ankylosing spondylitis enthesis score. LEI=Leeds enthesis index. CRP=C-reactive protein.*Secukinumab: 2 × 10 mg/kg. †Efficacy analysis dataset included only 29 participants, since one patient on secukinumab was excluded due to a dosing error. ‡Azathioprine or cyclosporine.

Table 1: **Baseline characteristics**

	Responders, n (%)	Response rate*	Difference *vs* placebo†	95% credibility interval†	Probability
Secukinumab‡§	14 (60·9%)	59·2%	34·7%	11·5–56·4%	99·8%
Placebo	1 (16·7%)	24·5%	..	..	..

ASAS=Assessment of SpondyloArthritis international Society criteria. *Means from the posterior beta ($0{\cdot}5+x$, $1+n-x$) distribution for secukinumab and beta ($11+x$, $32+n-x$) distribution for placebo, where x represents the number of responders and $n-x$ represents the number of non-responders in the corresponding treatment group. †Difference in response rates simulated from the posterior probability distributions of secukinumab and placebo. ‡Secukinumab: 2×10 mg/kg. §The efficacy dataset included only 23 of 24 patients in the secukinumab group, since one patient was excluded due to a dosing error.

Table 2: **Primary endpoint Bayesian analysis of ASAS20 responders at week 6**

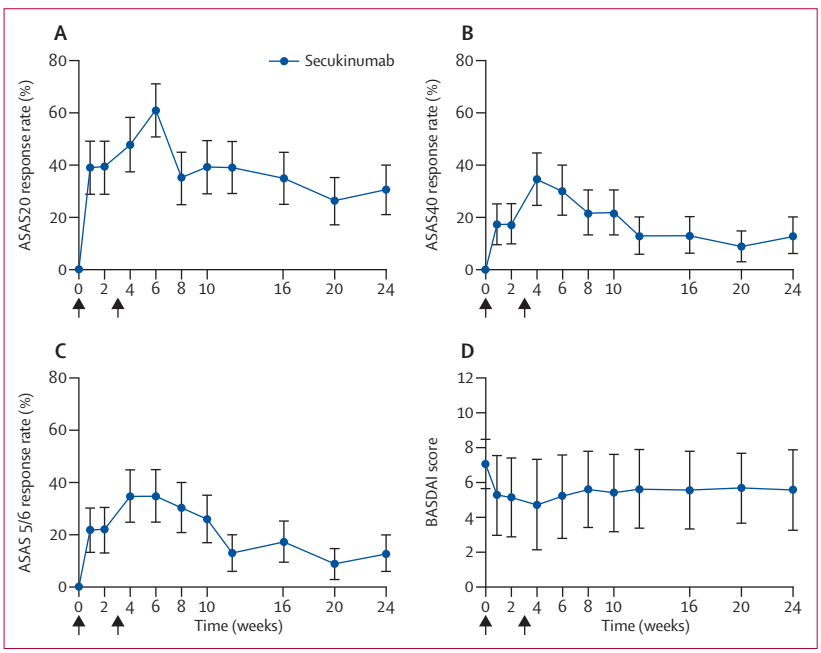

Figure 2: **Primary and secondary endpoints over time in patients receiving secukinumab 2×10 mg/kg**
Arrows below x-axis denote drug administration. Error bars in ASAS graphs represent mean (SE). Error bars in BASDAI graph represent mean (SD). ASAS=Assessment of SpondyloArthritis international Society criteria. BASDAI=Bath ankylosing spondylitis disease activity index.

into an informative prior distribution by means of the meta-analytic-predictive methodology described by Neuenschwander and colleagues.[30] This approach accounts for between-trial heterogeneity, since the data from the previous trials are downweighted compared with the data collected in this trial. The resulting prior distribution for the placebo response rate was equivalent to 43 patients (appendix). For the secukinumab response rate, an uninformative prior was used.

The predefined criterion to declare a positive proof-of-concept required a posterior probability of at least 95% that the ASAS20 response rate on secukinumab is larger than that on placebo. With data from 20 patients on secukinumab and five patients on placebo, the study showed a 90% probability of achieving proof-of-concept, assuming true response rates of 25% on placebo and 60% on secukinumab (appendix). Secondary and exploratory endpoint analyses were non-Bayesian and are summarised using descriptive statistics. Exploratory (post-hoc) analyses of MRI total scores and protein biomarkers were done to compare the change from baseline and post-treatment measurements (Wilcoxon signed-rank test).

Patients who dropped out of the study were considered non-responders in all planned ASAS assessments, irrespective of the reason for discontinuation. Comparisons between baseline and post-treatment measurements, as well as between ASAS responders and non-responders, applied Mann-Whitney tests.

An exploratory analysis of genetic data (13 polymorphisms shown to be associated with ankylosing spondylitis or in the target IL-17A gene region) was done with a subgroup of consenting patients taking secukinumab (N=22; appendix). The polymorphisms were tested individually for association with ASAS20 and ASAS40 response at week 6 using logistic regression models and with BASDAI using a linear regression model, with number of copies of the minor (less common) allele carried by the individual as the predictor and baseline BASDAI score as a covariate. A permutation test was done to account for small sample size and multiple comparisons of polymorphisms, with genotypes randomly permuted 250 000 times.

Role of the funding source

An academic advisory committee was involved in study design and data interpretation, together with authors from Novartis Institutes for Biomedical Research. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 37 patients with active ankylosing spondylitis who were screened, 30 were enrolled in the study and randomly assigned to receive intravenous 2×10 mg/kg secukinumab (n=24) or placebo (n=6) on day 1 and day 22 (figure 1). Baseline demographics were similar between the two groups (table 1). 22 of the 24 (92%) secukinumab-treated patients and three of the six (50%) placebo-treated patients reached week 6. Of the 25 patients still in the study at week 6, 15 in the secukinumab group and all three in the placebo group completed the study up to week 28. Patients who discontinued the study were considered to be non-responders for the efficacy analysis. Reasons for discontinuation were mainly unsatisfactory therapeutic effect, withdrawal of consent, and adverse events. Additionally, a dosing error led to one patient in the secukinumab group being excluded from the efficacy analysis but not from the safety analysis (as predefined by the protocol). Thus the efficacy analysis included 23 secukinumab patients and six placebo patients.

The primary efficacy outcome, ASAS20 response at week 6, was met by 14 (61%) of the 23 patients in the

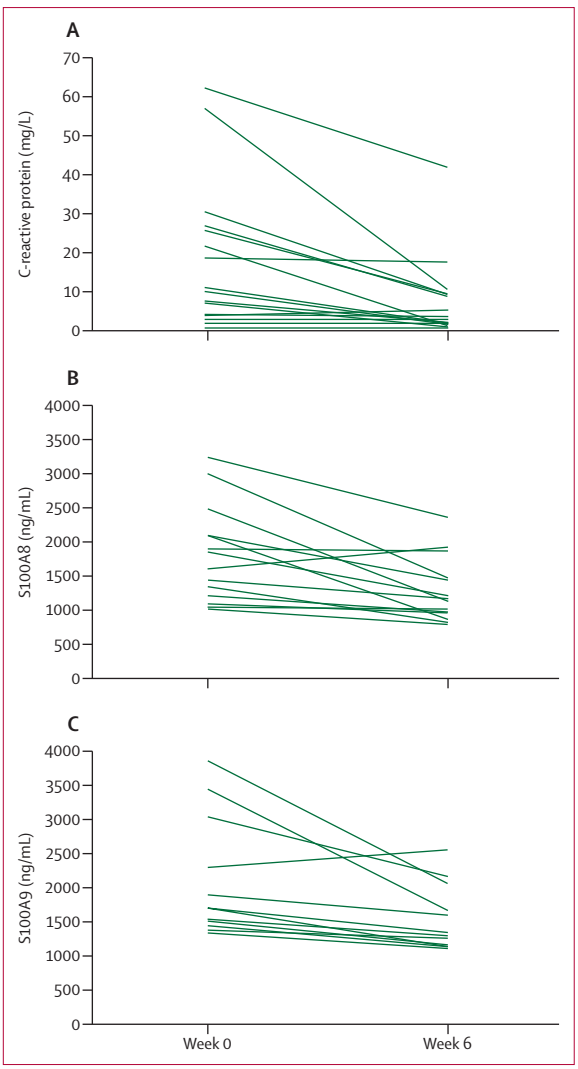

Figure 3: **Biological markers of response**
C-reactive protein (A), S100A8 (B), and S100A9 (C) levels at week 6, after secukinumab (2 × 10 mg/kg) administration at weeks 0 and 3.

secukinumab group and one (17%) of the six patients in the placebo group. Calculated response rates were 59% for the secukinumab group versus 24% for the placebo group. The observed placebo response rate was similar to the results obtained from the meta-analysis of eight comparable trials (26·5%).[29] Bayesian analysis (table 2) indicated that the probability of secukinumab inducing greater response rates than placebo was 99·8%.

The secondary efficacy endpoints, ASAS20, ASAS40, and ASAS5/6 response rates, and BASDAI scores up to week 28 are summarised in the appendix and shown for the secukinumab-treated patients in figure 2. Response rates for all ASAS measures and BASDAI were seen at week 6. Consistent with the loading dose regimen, there was a decreasing response rate by week 28. Clinically relevant improvement in quality of life, defined as a change of two or more points in ASQoL, was seen in 11 of 21 (52%) patients in the secukinumab group versus two of six (33%) patients in the placebo group at day 29. Additional ASQoL data are shown in the appendix.

Mean serum CRP levels decreased from 14·4 mg/L (SD 17·60) at baseline to 6·1 mg/L (9·23) at week 6 (p=0·03; figure 3A). Similarly, mean erythrocyte sedimentation rate decreased from 35·5 mm/h (SD 24·81) at baseline to 22·4 mm/h (16·27) at week 6 after secukinumab treatment (p=0·11; appendix). Mean levels of the inflammatory biomarker protein S100A8 decreased from 1818·7 ng/mL (SD 716·85) at baseline to 1286·2 ng/mL (478·37) at week 6 (p=0·01; figure 3B). Mean levels of the inflammatory biomarker protein S100A9 decreased from 2012·6 ng/mL (SD 835·46) at baseline to 1513·3 ng/mL (445·28) at week 6 (p=0·01; figure 3C). Additionally, ASAS20 response at week 6 was significantly correlated with both baseline levels of S100A8 (R=0·55) and A9 (0·39) and changes between baseline and week 6 levels of S100A8 (0·43) and A9 (0·28). Even stronger correlations were seen with the ASAS40 response at week 6 (R=0·40, 0·59, 0·52, and 0·64, respectively), indicating that clinical improvement was paralleled by a decrease in inflammatory parameters (appendix).

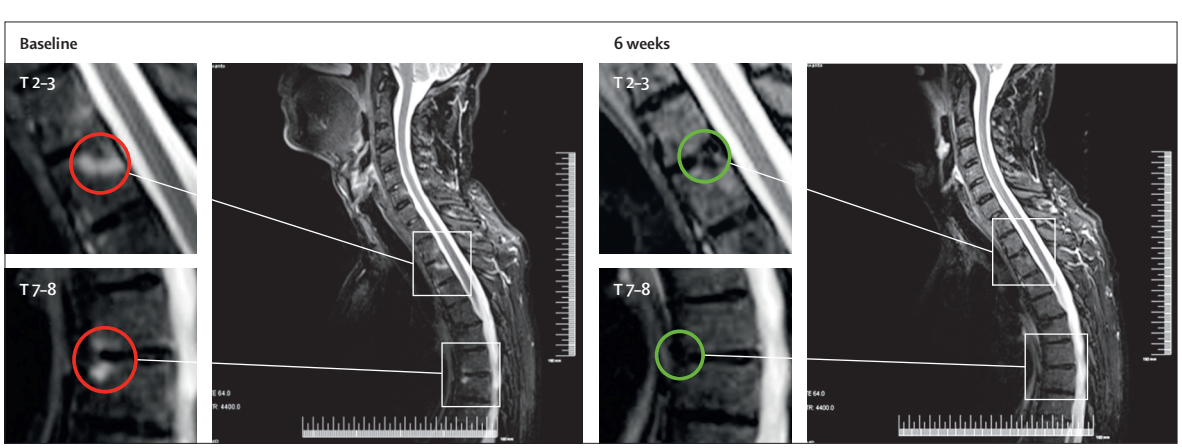

Figure 4: **Reduction of inflammation in thoracic (T2–T3) and (T7–T8) units at baseline and at week 6 in a patient treated with secukinumab**

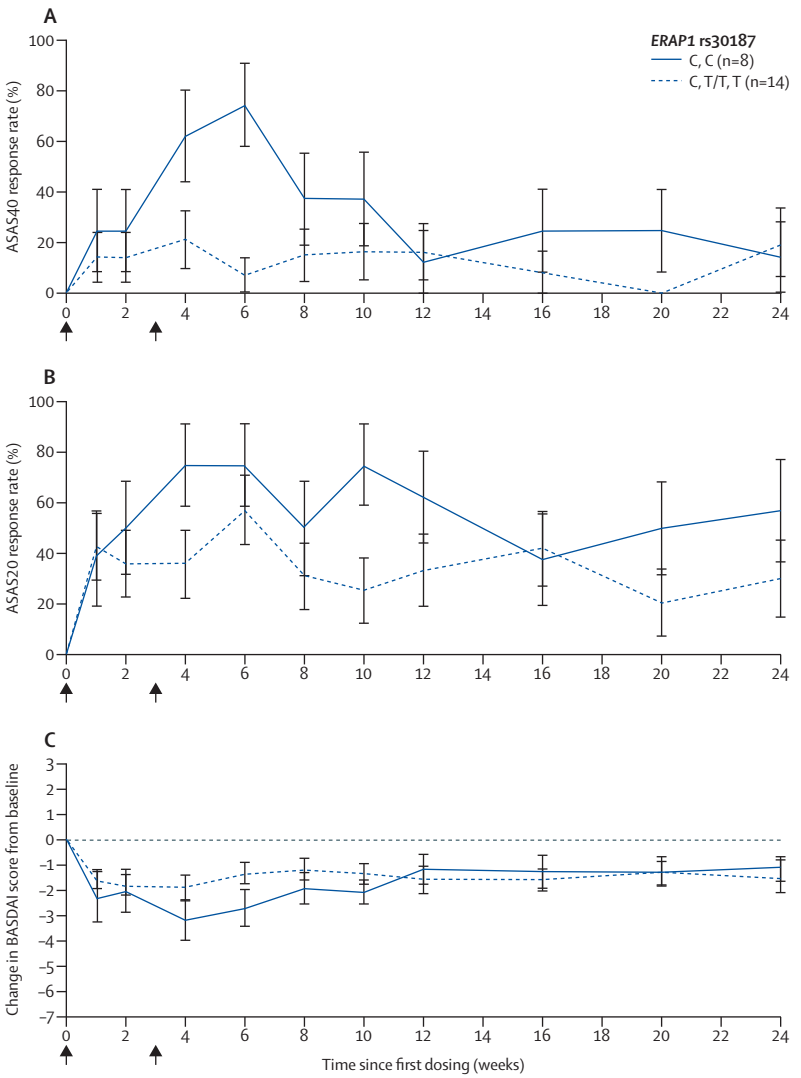

Figure 5: **Association of the rs30187 genotype for the *ERAP1* gene with mean ASAS40 response rates (A), mean ASAS20 response rates (B), and mean change in BASDAI from baseline (C) in patients treated with secukinumab**
Error bars in ASAS graphs represent mean (SE). Error bars in BASDAI graph represent mean (SD). Polymorphisms were tested individually for association with ASAS40 and ASAS20 at week 6 using a logistic regression model, and with BASDAI at week 24 using a linear regression model, with number of copies of the minor (less common) allele carried by the individual as the predictor and baseline BASDAI score as a covariate. Minor allele/AS risk allele=T. Major allele=C. ASAS=Assessment of SpondyloArthritis international Society criteria. BASDAI=Bath ankylosing spondylitis disease activity index. CRP=C-reactive protein. SE=standard error.

	Secukinumab (N=24)	Placebo (N=6)
All adverse events		
Patients with an adverse event	23 (95·8%)	6 (100·0%)
Most frequent adverse events		
Headache	7 (29·2%)	..
Nasopharyngitis	7 (29·2%)	..
Nausea	4 (16·7%)	1 (16·7%)
Diarrhoea	4 (16·7%)	..
Pyrexia	4 (16·7%)	..
Back pain	3 (12·5%)	1 (16·7%)
Fatigue	3 (12·5%)	1 (16·7%)
Paraesthesia	3 (12·5%)	1 (16·7%)
Arthralgia	3 (12·5%)	..
Influenza	3 (12·5%)	..
Oropharyngeal pain	3 (12·5%)	..
Dizziness	2 (8·3%)	1 (16·7%)
Oral herpes	2 (8·3%)	1 (16·7%)
Pruritus	2 (8·3%)	1 (16·7%)
Abdominal pain, upper	2 (8·3%)	..
Bronchitis	2 (8·3%)	..
Cough	2 (8·3%)	..
Dysgeusia	2 (8·3%)	..
Gastroenteritis	2 (8·3%)	..
Mouth ulceration	2 (8·3%)	..
Myalgia	2 (8·3%)	..
Rhinitis	2 (8·3%)	..
Adverse events related to infections		
Nasopharyngitis	7 (29·2%)	..
Influenza	3 (12·5%)	..
Oral herpes	2 (8·3%)	1 (16·7%)
Gastroenteritis	2 (8·3%)	..

Data are n (%). *Secukinumab: 2×10 mg/kg.

Table 3: **Most frequent adverse events seen in more than 5% of patients on secukinumab**

Findings from direct visualisation of the axial inflammatory lesions by MRI (figure 4) were consistent with the clinical effects and results seen for the protein measures. The mean MRI scores decreased from 9·2 (SD 8·87) at baseline to 6·6 (6·56) at week 6 (p=0·10) and 5·7 (6·20) at week 28 (p=0·16) in the secukinumab group (appendix). The mean MRI scores were unchanged in the placebo group: 20·6 (SD 20·18) at baseline, 21·0 (24·56) at week 6, and 19·0 (19·33) at week 28.

For the genetic biomarkers, a non-synonymous SNP of the *ERAP1* gene, rs30187, which leads to significantly reduced endopeptidase activity in vitro and is associated with protection against ankylosing spondylitis,[27,31] had a highly significant association with ASAS40 at week 6 in secukinumab-treated patients (nominal p=$8·14\times10^{-5}$ and empirical p=0·004 in permutation test after correction for multiple comparisons). The association of SNP rs30187 with the ASAS40 response was consistent over time (figure 5A). The analysis also yielded a significant p value when restricted to the HLA-B27 positive subset of patients (n=17, p=0·0022 for association between rs30187 and ASAS40 at week 6). A similar, but weaker association with ASAS20 was seen for SNP rs30187 (figure 5B), but only a minor association was seen with BASDAI changes (figure 5C, appendix). Supporting the notion that these SNPs have a biological effect, the carriers of the *ERAP1* risk alleles of rs30187 or rs27434 typically showed higher levels of *ERAP1* gene expression, whereas homozygous non-carriers mostly showed lower transcript levels

(appendix). Additionally, an association with BASDAI changes over time was seen for *IL23R* polymorphisms rs11209032 and rs2201841. However, no association of *IL23R* polymorphisms with ASAS40 was seen (appendix).

Data for all randomised patients were used for the safety analysis (table 3). Since this study was not powered for statistical comparisons between the secukinumab (N=24) and placebo groups (N=6), only descriptive analyses are provided. The numbers and rates of patients with at least one adverse event were similar between secukinumab (23 patients [96%]) and placebo (6 [100%]). The most frequently reported adverse events on secukinumab were nasopharyngitis and headache (table 3).

The incidence of infections was higher for secukinumab than for placebo (table 3). One serious adverse event was seen in the secukinumab group: at week 9 a patient developed an abscess of the foot caused by *Staphylococcus aureus* that required antibiotic therapy and hospitalisation for surgical drainage, and the patient was discontinued from the study. Several cases of leucopenia and neutropenia were reported; all were graded Common Terminology Criteria grade 1, with no apparent temporal relation to infections. No evidence of formation of antidrug antibodies or clinical signs of immunogenicity were noted.

***Panel:* Research in context**

Systematic review

We searched the PubMed database, using the terms "ankylosing spondylitis", "biologic therapy", and "IL-17", for English-language articles published up to April, 2013. IL-17 has been proposed to be a key inflammatory cytokine in ankylosing spondylitis,[3–13] the prototypical form of spondyloarthritis. The IL-17 blockers secukinumab (anti-IL-17A), ixekizumab (anti-IL-17A), and brodalumab (anti-IL-17RA) have shown efficacy in phase 2 trials in psoriasis,[15–19] a spondyloarthritis-related inflammatory skin disease. A trend towards clinical efficacy was recently reported for secukinumab in psoriatic arthritis, a distinct but related form of spondyloarthritis. The current report describes the first clinical trial assessing the safety and efficacy of IL-17 blockade in ankylosing spondylitis.

Interpretation

Treatment with secukinumab induced a significant and clinically relevant reduction of disease activity in active ankylosing spondylitis as early as 6 weeks after initiation of treatment. IL-17 blockade could be the first therapeutic alternative to TNF blockade in NSAID-resistant ankylosing spondylitis.

Discussion

Secukinumab was associated with rapid and significant reduction in the signs and symptoms of active ankylosing spondylitis in patients with inadequate response to NSAIDs.

60% of patients in the secukinumab group reached the primary endpoint of ASAS20 responses at week 6, indicating a 99·8% probability that secukinumab was more effective than placebo (table 2, figure 2). Favourable changes in secondary clinical outcomes, including quality-of-life measures, further supported clinical efficacy.

Secukinumab treatment was associated with a rapid and significant decrease in acute-phase parameters. Since CRP and S100 proteins were only weakly correlated, S100 proteins might have added value as markers of inflammation. There were also decreased MRI scores for spinal inflammatory lesions. The clinical response to secukinumab was also significantly associated with genetic polymorphisms in *ERAP1*, and showed a trend towards association with polymorphisms in *IL23R*. Although these data suggest that both genes could be associated with a better clinical response to secukinumab, future experiments are needed to clarify the potential role of these disease-risk alleles in the response to an anti-IL-17 therapy. Nevertheless, our findings indicate a strong association between pathway-related genetic risk factors and clinical response to therapeutic targeting of the pathway in immune-mediated inflammatory disease. Larger and more extensive analysis of the biomarker value of *ERAP1* and *IL23R* SNPs for the prediction of clinical response are needed. Taken together, these data provide evidence that IL-17 blockade modulates clinical and biological signs of inflammation and might therefore be a valid therapeutic approach in ankylosing spondylitis. Biomarkers related to antigen processing and presentation, as well as to the IL-23/IL-17 axis, could be useful for prediction of outcomes.

To the best of our knowledge, this study is the first to provide evidence for clinical efficacy of a non–TNF-blocker targeted therapy in ankylosing spondylitis (panel). Recent trials with abatacept, IL-6 blockade, and the small molecule apremilast, failed to show significant clinical efficacy in ankylosing spondylitis.[25] Rituximab plus methylprednisolone showed modest clinical effects in a small open study.[32] Ustekinumab, a fully human monoclonal antibody directed against the p40 subunit shared by IL-12 and IL-23, is currently in phase 2 trials (ClinicalTrials.gov number NCT01330901). Several other compounds (including tofacitinib, a Janus kinase 3 inhibitor [not yet listed in ClinicalTrials.gov]) have entered clinical trials, with no or mixed results reported so far.[25]

IL-17 blockade is currently being explored as a therapeutic strategy for various immune-mediated inflammatory diseases. Randomised controlled trials have reported consistent clinical efficacy of this approach in psoriasis,[15–19] a disease that shares certain *IL23R* genetic associations with Crohn's disease and ankylosing spondylitis. In Crohn's disease, however, anti-IL-17A blockade with secukinumab was not superior to placebo,[28] and two trials with an IL-17R antagonist (AMG 827) were stopped (ClinicalTrials.gov numbers NCT01199302 and

NCT01150890), indicating that clinical outcomes of IL-17 inhibition could vary among conditions that share genetic risk factors related to the IL-23/IL-17 axis. Therefore, there was good reason to design and undertake a proof-of-concept trial to investigate the safety and potential efficacy of secukinumab in patients with active ankylosing spondylitis.

To make the best use of the existing information on placebo response rates (based on eight previous trials of biological agents in active ankylosing spondylitis), these historical data were integrated into the primary endpoint analysis using Bayesian methods, allowing us to reduce the number of placebo patients required.[29] The number of treated patients (N=24) was similar to the numbers included in other proof-of-concept randomised trials with TNF-blockers in ankylosing spondylitis (N=35) and spondyloarthritis (N=20).[2,33] On the basis of previous data in psoriasis and rheumatoid arthritis,[15] we set the primary endpoint at week 6 (after only two administrations of drug or placebo). A set of inflammatory, imaging, and pharmacogenetic outcomes were included in the study to substantiate clinical data with biological evidence.

Study limitations included the inability to undertake sufficiently powered statistical comparisons for the secondary efficacy endpoints because of the limited placebo sample size. Tender and swollen joint counts and enthesitis scores were planned as secondary endpoints, but were seen at such low frequencies that we were unable to assess the potential treatment effect of secukinumab. The exploratory biomarker analyses in this study were also based on small sample sizes; hence the possibility that the observed differences occurred by chance cannot be excluded. Small sample sizes could also explain the different strength of associations at different timepoints, and between assessments. For the MRI analyses, the higher baseline scores for inflammation reported in the placebo group might represent a confounding factor in interpreting the treatment effect seen for secukinumab. However, recent studies in patients receiving anti-TNF agents[34,35] have indicated that higher baseline MRI scores do not identify therapeutic non-responders, but rather identify those patients who are candidates for better response to anti-inflammatory treatment, a hypothesis supported by our results. A confounding effect of background medication on transcriptional profiles cannot be ruled out. A post-hoc analysis of patient subgroups according to previous TNF inhibitor exposure was done but was compromised due to an inadequate number of patients (and thus not included in this paper).

The preliminary safety profile from our trial was similar to those reported in larger phase 2 studies with secukinumab in other indications, in regards to both the type and frequency of adverse events.[15,18,19,28,36] However, the small size of our study cohort did not permit definitive conclusions regarding the safety of secukinumab. Larger and longer-term studies are needed to confirm our findings.

Contributors

DB contributed to study design, data collection, data analysis, data interpretation, and writing and review of the manuscript. XB contributed to MRI reading and interpretation, data interpretation, and review of the manuscript. JS, DvdH, IM, JMvL, RL, HK, JP, and DL contributed to data collection, data interpretation, and review of the manuscript. PE contributed to data collection, data interpretation, and writing and review of the manuscript. PW contributed to data analysis and review of the manuscript. JB and JWo contributed to data collection, data analysis, data interpretation, and writing and review of the manuscript. JWe and YL contributed to data collection, data analysis, data interpretation, and review of the manuscript. AB contributed to data analysis, and writing and review of the manuscript. SB contributed to data collection and review of the manuscript. YAW designed the genetic analysis used in the study and contributed to the review of the manuscript. APB contributed to data collection, data interpretation, review of the manuscript, and study oversight. SG contributed to data analysis, data interpretation, and review of the manuscript. AMW contributed to study design, data interpretation, and review of the manuscript. WH contributed to study design, data analysis, data interpretation, and writing, review, and final approval of the manuscript.

Conflicts of interest

DB has participated in advisory boards for Abbott, BMS, Boehringer Ingelheim, Janssen-Cilag, MSD, Novartis, Pfizer, Roche, and UCB, and has received unrestricted study grants from Abbott, Centocor, Janssen-Cilag, MSD, Novartis, and Pfizer. XB has received consulting fees and research grants from Abbott, Centocor, Janssen, MSD, Novartis, Pfizer, Schering-Plough, UCB, and Wyeth. JB has served on advisory boards for, and received consulting fees or research grants from Abbott, Amgen, BMS, Celltrion, Centocor, Chugai, Eli Lilly, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, and UCB. JS has served on advisory boards for Novartis. PE has served on advisory boards for Abbott, BMS, Merck, Novartis, Pfizer, Roche, and UCB. DvdH has received consulting fees or research grants from Abbott, Amgen, BMS, AstraZeneca, Centocor, Chugai, Eli Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, and Wyeth. IM has served on advisory boards for Novartis. JMvL has received consulting and speaker's fees and/or research grants from Abbott, Actelion, BMS, Pfizer, and Roche. RL has received consulting fees or research grants from Abbott, Amgen, BMS, Centocor, GSK, Merck, Novartis, Pfizer, Roche, Schering-Plough, UCB, and Wyeth. PW has received consulting and speaker's fees from Abbott Laboratories and unrestricted educational grants from Abbott Laboratories and Pfizer, and is a trustee and executive committee member of the National Ankylosing Spondylitis Society. JWo has served on advisory boards for Novartis. JWe, YL, and SB are employees of Novartis. AB, DL, YAW, and AMW are employees of and own stock in Novartis. APB and SG were employees of Novartis at the time this paper was written and owned stock in Novartis during this time. WH is an employee of and owns stock options in Novartis. The other authors declare that they have no conflicts of interest.

Acknowledgments

We thank Vasundhara Pathak, Novartis Healthcare, Hyderabad, India, for support in the writing of this manuscript. Editorial assistance was provided by BioScience Communications, New York, NY, USA, supported by Novartis Pharma AG, Basel, Switzerland.

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