Secukinumab's effect on structural damage progression in psoriatic arthritis: longitudinal mixture modelling of FUTURE-1 and FUTURE-5

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Abstract

Objective

Peripheral and axial manifestations of psoriatic arthritis (PsA) can lead to irreversible structural damage and chronic disability. Our objective was to explore predictors of radiographic progression and to increase our understanding of treatment effects in subgroups of patients with different rates of structural damage progression.

Methods

We analysed data from two large Phase-3 trials of secukinumab in PsA patients, FUTURE-1 (NCT01392326, n=606) and FUTURE-5 (NCT02404350, n=996), where different posologies ranging from 75 mg to 300 mg were used. We applied a longitudinal Bayesian mixture model with random effects to account for the variability in the repeated radiographic assessments. "Fast progressors" were defined post hoc as patients with a 50% model-estimated probability to progress at least 0.5 mTSS/year faster than an average patient.

Results

Higher baseline inflammation and higher body weight were identified as significant predictors of radiographic progression (multivariate model). Model-estimated structural damage progression in an average patient treated with secukinumab 150 mg subcutaneous (s.c.) was slower (0.04 mTSS/year; 95% CI -0.28, 0.34) compared to a patient treated with placebo (0.94 mTSS/year; 95% CI 0.45, 1.45). According to the model, the subgroup of "fast progressors" (hsCRP ≥26 mg/L, body weigth ≥94 kg, inadequate response to prior anti-TNF-alpha, structural damage ≥42 mTSS) treated with secukinumab 150 mg s.c. progressed at 0.56 mTSS/year (95% CI 0.02, 1.09) and 1.46 mTSS/year (95% CI 0.81, 2.11) when treated with placebo.

Conclusions

Greater systemic inflammation and higher body weight at baseline were identified as significant predictors of progression. Even patients with fast radiographic progression could experience a beneficial effect with secukinumab that holds promise to prevent further mobility loss.

Key words

psoriatic arthritis, secukinumab, IL-17 inhibitor, radiographic progression

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Introduction

Psoriatic arthritis (PsA) is a chronic, heterogenous systemic inflammatory disease with an estimated global prevalence of about 133 cases per 100,000 population and considerable geographic variability (1). The disease affects multiple features, including peripheral joints, connective tissues, and the axial skeleton (2, 3). Symptoms include peripheral arthritis, dactylitis, enthesitis, skin and nail psoriasis, and axial disease (3, 4).

If not treated effectively, PsA can lead to irreversible damage to peripheral joints and spine, causing life-long pain and disability that have a negative impact on even simple tasks (5, 6) Physical function and Quality of Life (QoL) of PsA patients have been shown to be negatively affected by joint structural damage; the signs and symptoms usually progress from pain and swelling to loss of mobility and eventually function (7). A survey of affected patients has revealed a substantial impact on QoL and productivity (8).

Recent advances in the molecular and physiological understanding of the disease have led to the development of new treatment options (9) with the field experiencing a shift from the identification of new treatments to a better understanding of the heterogeneous nature of the disease and now aiming at improved stratification of patients for optimised treatment strategies (10). These efforts are hampered by substantial diversity in symptomatology and treatment response. There is thus a substantial unmet need for better understanding of clinically heterogeneous patient subgroups and predictors of treatment response (11).

We herein investigate the progression of structural damage, which includes bone erosion and joint space narrowing occurs in up to 47% of PsA patients at a median interval of two years (12). The FUTURE-1 (13) and FUTURE-5 (14) randomised clinical trials demonstrated that secukinumab, an anti-interleukin-17A monoclonal antibody, was effective in the treatment of PsA signs and symptoms, as well as inhibition of structural damage progression and improvement of physical function and QoL.

The objective of the current modelling study was to identify predictors of progression in these trials and to increase our understanding of the effect of secukinumab on the inhibition of structural damage in PsA in subgroups of patients with different underlying rates of progression.

Methods

Data sources

We included combined data from the FUTURE-1 (13) (clinicaltrials.gov identifier NCT01392326) and FUTURE-5 (14) (clinicaltrials.gov identifier NCT02404350) Phase 3 randomised controlled trials, investigating the effect of secukinumab at different posologies. These studies were designed, performed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki. The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each participating centre. Informed consent was obtained in writing from all participating patients.

Patients were aged ≥18 years, fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR), and had active disease, which was defined as three or more tender joints and three or more swollen joints, despite previous treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs, or TNF inhibitors. The concomitant use of oral glucocorticoids (at a dose of ≤10 mg per day of prednisone or its equivalent) and methotrexate (at a dose of ≤25 mg per week) were permitted, provided the dose was stable. Patients who had previously received anti-TNF therapy were required either to have had an inadequate response or to have stopped treatment because of side effects. For patients who had received anti-TNF agents, a washout period of 4 to 10 weeks before randomisation was required.

In FUTURE-1, patients were treated with secukinumab 10 mg/kg intravenously at baseline, and at weeks 2 and 4,

followed by 75 mg or 150 mg subcutaneously every 4 weeks from week 8, or with a matching placebo. In FUTURE-5, patients received secukinumab every 4 weeks either at 300 mg or 150 mg (with a loading dose at baseline, and at weeks 1, 2 and 3, or without), or with a matching placebo. All placebo patients were re-randomised to secukinumab either at week 16 or 24 depending on their ACR20 response, and further followed until 104 weeks. Data from FUTURE-1 were available until 104 weeks follow up, while FUTURE-5 is still ongoing and therefore only contributed data until up to 24 weeks follow-up. Because the goal of this study was to model structural damage progression, only patients with at least 2 measurements of structural damage were included. The total number of patients contributing data was n=1465 (539 from FUTURE-1 and 926 from FUTURE 5).

Modelled outcome

Structural damage was measured using the Total Sharp Score (mTSS), the modified the van der Heijde method and assessed by two independent central assessors who were blinded to patient treatment assignment and acquisition sequence (15). The modelled outcome was yearly change in structural damage (ΔmTSS/year) across all available x-ray measurements, typically taken at 0, 16/24, 52 or 104 weeks from randomisation. The placebo arm was included until week 16/24 and removed from the modelling thereafter. The reported model output was mean yearly change in structural damage. CIs are 95% Bayesian Credibility Intervals.

Modelling methods

We used a Bayesian mixture model with random effects to identify risk factors for structural damage progression in PsA and to test how structural damage progression may be affected by treatment with secukinumab, depending on the patients' characteristics. The model structure is described in detail elsewhere (16). This model assumes that the observed structural damage is a product of probability and magnitude of progression. The model allows to account for the fact that majority of patients do not progress within a short window of observation in a clinical trial, due to a slow underlying disease progression in most individuals, receiving active treatment and relatively low sensitivity of x-ray images (see the distribution Fig. 1). This model has previously been shown to perform better than linear model (16). The random effects were included to account for inter-patient variability in the magnitude of progression due to repeated measurements, as well as a separate noise term to account for the fact that each set of x-rays was assessed multiple times. The model was estimated using a Bayesian approach and utilising non-informative priors for all parameters. Stan (http://mc-stan.org) was used in R (through package rstan) for Bayesian inference. The model converged well at 2,000 iterations per chain, 6 chains per model, with computation time less than 10 minutes.

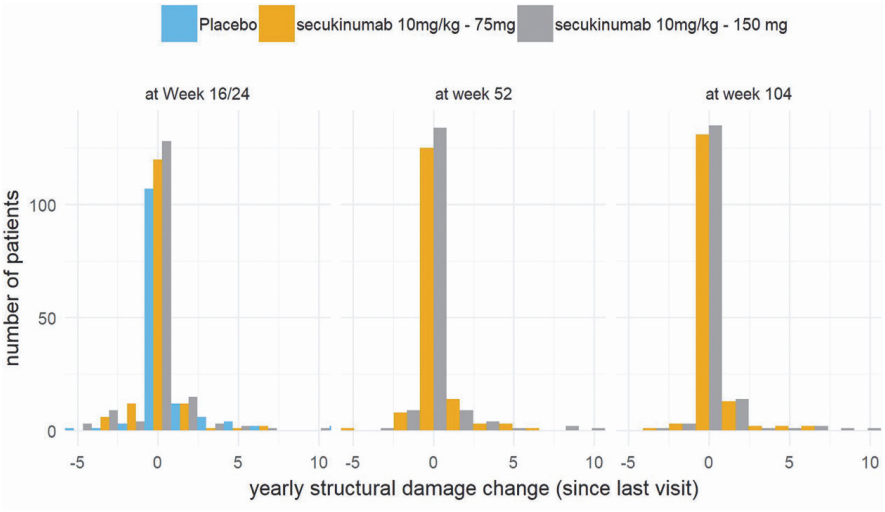

Fig. 1. Change in structural damage in PsA (TSS), standardised per year.
Source: FUTURE-1 Campaign 2 data, X axis truncated at (-5, 10).

Exposure to secukinumab

In order to evaluate treatment effect across treatment arms with different posologies, proxy exposure to secukinumab was used in the model. It was defined as plasma concentration of secukinumab [ng/mL], averaged over a period of time (A-AUC), then log-transformed and z-standardised. To achieve interpretation in terms of posologies currently used in the clinical practice (150 mg s.c. with and without loading, and 300 mg s.c. without loading) the average exposure achieved in the corresponding treatment arm was assumed for the calculation of the model-predicted progression.

Covariate selection

Covariates considered as potential predictors were identified based on a literature review, clinical knowledge, data availability, and the correlation structure between them. The final list of covariates included: age [year], weight [kg], gender [female/male], current smoking status [yes/no], time since PsA diagnosis [years], prior exposure to anti-TNF-α [naïve/inadequate responder], concomitant use of methotrexate [yes/no], C-reactive protein (CRP) [mg/L], baseline structural damage at randomisation [mTSS], Quality of Life [PsAQoL], functional disability [HAQ-DI], Leeds Enthesitis Index [0–6 in FUTURE-5, 0–4 in FUTURE-1 where medial femoral condyles left and right were not assessed], nail manifestation - presence of dactilitis at baseline [yes/no], number of tender and swollen joints count [out of 76 and 78 assessed, respectively], and skin manifestation - Psoriasis Area and Severity Index [PASI] score. All covariates were measured at baseline and z-standardised by subtracting the mean and dividing by standard deviation (SD).

Fast progressors

A profile of 'fast progressors' was defined based on four predictors from

the multivariate model (inflammation, body weight, prior treatment, baseline mTSS) as a patient with baseline characteristics associated with 50% model-estimated probability of progressing 0.5 mTSS/year faster than an average/reference patient.

Results

Baseline characteristics

Table I summarises the baseline characteristics of patients in the two trials. Because the goal of this study was to track and model structural damage progression, only patients with at least 2 measurements of structural damage were included.

Predictors of progression and treatment effect

Table II contains estimates of the yearly structural damage progression in PsA depending on a patient's characteristics. Two types of results were presented: Model-estimated, bi-variate association between structural damage and covariates, and the results of a multivariate model. The column labelled "Mean" contains the point estimate of the contribution that each covariate makes towards the yearly structural damage progression, expressed on the mTSS scale.

Within a series of bi-variate models, several predictors of structural damage were identified which contributed to faster structural damage progression. The strongest predictor was prior inadequate response to anti-TNF-α, associated with additional progression of 0.45 mTSS/year (CI 0.14, 0.76). It was followed by inflammation, with 0.35 additional mTSS/year (CI 0.22, 0.50), per each additional SD in hsCRP (24 mg/L). The third predictor was baseline structural damage, with additional 0.23 mTSS/year (CI 0.09, 0.36), per each additional 43 mTSS at baseline. Similar trends existed for higher baseline functional impairment (HAQ-DI) and higher weight, where each additional SD in these metrics were associated with additional progression of 0.13 (CI -0.01, 0.28) and 0.11 mTSS/year (CI -0.03, 0.26), respectively.

In the multivariate model including all covariates and treatment effect with

Table I. Baseline characteristics of the patient population selected from the Phase-3 RCT FUTURE-1 and FUTURE-5 for modelling structural damage progression in PsA.

	FUTURE-1 (n*=539)	FUTURE-5 (n*=926)
Treatment arm (n(%))		
placebo**	167 (31)	286 (31)
secukinumab 10mg/kg i.v. - 75 mg s.c.	183 (34)	-
secukinumab 10mg/kg i.v. - 150 mg s.c.	189 (35)	-
secukinumab 150 mg s.c. with loading	-	213 (23)
secukinumab 150 mg s.c. without loading	-	210 (23)
secukinumab 300 mg s.c with loading	-	217 (23)
Patient's characteristics (n (%))		
gender = male	249 (46)	471 (51)
current smoker = yes	104 (19)	176 (19)
prior exposure to anti-TNFα = yes	151 (28)	265 (29)
methotrexate use at baseline =yes	329 (61)	472 (51)
dactilitis = yes	233 (43)	361 (39)
Patient's characteristics (mean (SD))		
Number of measurements of change in structural damage	3.79 (1.70)	1.09 (0.28)
age [years]	48.88 (11.71)	48.58 (12.37)
time since diagnosis [years]	7.72 (8.33)	6.56 (7.28)
structural damage [TSS]	23.08 (50.47)	14.29 (32.54)
hsCRP [mg/L]	13.97 (21.18)	12.48 (24.41)
HAQ-DI	1.22 (0.66)	1.25 (0.63)
PsA QoL	10.37 (5.91)	10.16 (5.98)
Leeds Enthesis Index***	1.37 (1.38)	1.66 (1.80)
PASI score	8.25 (10.71)	7.09 (9.34)
weight [kg]	82.85 (20.71)	83.24 (19.38)
number of tender + swollen joints	38.33 (26.79)	32.33 (23.10)

*patients with at least 2 measurements of structural damage **until 16/24 weeks, depending on the clinical response ***In FUTURE-1 four sites were assessed (lateral epicondyles of the humerus left and right, and Achilles tendon insertions left and right).

Table II. Results of the Bayesian 2-state inference model in PsA – contribution of covariates to estimated yearly structural damage progression assessed by modified total Sharp Score (mTSS).

Treatment/Covariate	Bivariate model mean (95% CI)	Multivariate model mean (95% CI)
Intercept		0.07* (-0.25, 0.38)
Placebo		0.87* (0.50, 1.27)
Treatment with secukinumab (average daily exposure) (per 1 SD increase**)		-0.11 (-0.22, 0.01)
Female (ref. male)	-0.11 (-0.39, 0.19)	0.05 (-0.24, 0.34)
Current smoker (ref. not smoking)	-0.08 (-0.44,0.27)	-0.03 (-0.37, 0.31)
Anti-TNFα inadequate responder (ref. naïve)	0.45* (0.14 ,0.76)	0.23 (-0.11, 0.56)
Methotrexate use at baseline (ref. not using)	0.02 (-0.12, 0.16)	-0.04 (-0.31, 0.23)
Dactylitis (ref. no dactylitis)	0.16 (-0.11, 0.44)	0.12 (-0.16, 0.40)
Age (per 1 SD increase)	-0.03 (-0.17, 0.12)	-0.05 (-0.20, 0.10)
Time since diagnosis (per 1 SD increase)	0.05 (-0.11, 0.19)	-0.04 (-0.17, 0.09)
baseline structural damage (per 1 SD increase)	0.23* (0.09, 0.36)	0.14 (-0.23, 0.51)
hsCRP (per 1 SD increase)	0.35* (0.22, 0.50)	0.23* (0.09, 0.37)
HAQ-DI (per 1 SD increase)	0.13 (-0.01, 0.28)	0.06 (-0.13, 0.26)
PsA QoL (per 1 SD increase)	-0.01 (-0.15, 0.14)	-0.12 (-0.29, 0.05)
Leeds Enthesis Index*** (per 1 SD increase)	0.02 (-0.12, 0.16)	0.00 (-0.14, 0.13)
PASI (per 1 SD increase)	0.00 (-0.14, 0.15)	-0.02 (-0.15, 0.12)
Weight (per 1 SD increase)	0.11 (-0.03, 0.26)	0.19* (0.03, 0.34)
Number of tender + swollen joints (per 1 SD increase)	0.09 (-0.05, 0.24)	0.00 (-0.13, 0.14)

*95% interval for the coefficient does not contain 0 **log(9500 ng/mL) ***In FUTURE-1 four sites were assessed (lateral epicondyles of the humerus left and right, and Achilles tendon insertions left and right).
Source: modelling of FUTURE-1&-5 RCTs, pooled.

secukinumab, only two of these covariates retained statistical significance: inflammation, with each additional SD in hsCRP associated with faster progression by 0.23 mTSS/year (CI 0.09, 0.37), and body weight, with each additional 20 kg associated with additional 0.19 mTSS of yearly progression (CI 0.03, 0.34). However, a trend existed also for prior exposure to anti-TNFα (additional 0.23 mTSS/year (CI -0.11, 0.56) as compared with anti-TNF-α naïve patients) and for baseline structural damage (additional 0.14 mTSS/year (CI -0.23, 0.51), per each SD increase).

Identification of fast progressors

Table III presents these characteristics, together with model-estimated progression for fast progressor patients, compared to an average / reference patient.

According to the model, an "average," untreated patient progressed at a rate of 0.94 mTSS/year (CI 0.45, 1.45). A patient treated with secukinumab was estimated to progress less, at a rate of 0.04 mTSS/year (CI -0.28, 0.34), when the exposure equivalent to 150mg without s.c. load was reached. High exposure to secukinumab, such as in the 300 mg with s.c. load treatment arm of the FUTURE-5 trial, was associated with a progression rate of 0.00 mTSS/year (CI -0.33, 0.31).

Having hsCRP of at least 26 mg/L, baseline structural damage of at least ~42 points, weight higher than 94 kg and prior inadequate response to anti-TNF-α treatment resulted in 50% probability of progressing 0.5 mTSS/year faster than an average patient (in the analysed dataset). A total of 17 patients (~1%) met all four of these criteria in the PsA modelling dataset. The model predicted that meeting these four criteria was associated with a progression of 1.46 mTSS/year (CI 0.81, 2.11), and that this fast progression rate could be reduced to 0.56 mTSS/year (CI 0.02, 1.09), when the patient achieved an average secukinumab exposure that corresponded to 150 mg s.c. with loading, and to 0.52 mTSS/year (CI -0.03, 1.04) under high exposure, which corresponded to secukinumab's 300 mg dose regimen.

Table III. Subgroup analysis of patients who progress at different rates.

	Average patient	Fast progressor***
Definition: patient's characteristics at baseline		
Inflammation, hsCRP (mg/L)	~13.10	≥ 26
Body weight (kg)	~83	≥ 94
Prior anti-TNF-α exposure	naïve	experienced with inadequate response
Structural damage (mTSS)	~18	≥ 42
% of patients in the modelling dataset	-	~1%
Results: Model estimated progression rate (TSS/year with 95% CI)		
Placebo	0.94 (0.45, 1.45)	1.46 (0.81, 2.11)
Secukinumab 150 mg without s.c. load*	0.04 (-0.28, 0.34)	0.56 (0.02, 1.09)
Secukinumab 300 with s.c. load**	0.00 (-0.33, 0.31)	0.52 (-0.03, 1.04)

*assuming exposure like in 150 mg without s.c. load, **assuming exposure like in 300 mg + s.c. load, ***patient with 50% model-estimated probability to progress **0.5** mTSS/year faster than an average patient.

Discussion

Summary of findings and alignment with previous studies

Factors at baseline associated with further fast radiographic progression were found to be higher inflammation (hsCRP) and higher body weight. Similar trends were observed for prior exposure to anti-TNF-α, and higher baseline structural damage. Elevated inflammation at baseline has previously been identified as one of the most important predictors of future radiological progression (5). Our study further identified body weight as a predictor of radiographic progression. This is consistent with a previous study that identified body mass index (BMI) larger than 25 as a predictor of arthritis in patients with psoriasis (17). In contrast to previous studies (18), our model did not identify the number of tender swollen joints as a predictor. However, consistently with other studies we found the distribution of this variable to be highly skewed [*e.g.* with median of 1 and range from 0–28 swollen joints in hands and feet (19)], rendering it susceptible to the influence of relatively few patients. It is thus possible that other studies overestimated this effect, that our study was underpowered to detect a true effect, or that the effect is driven by a subpopulation of patients that was not recruited into the RCTs included herein at sufficient numbers. Furthermore, the model demonstrated that it was feasible to identify subgroups of patients with high risk of fast progression (*i.e.* fast progressors).

The model results are consistent with and provide further insights into the inhibition of structural damage progression at group level from FUTURE-1 (20) and FUTURE-5 (14) studies. The model indicated that secukinumab was effective at inhibiting structural damage progression down to even 0.00 (CI -0.33, 0.31) mTSS/year in a patient using the dose 300 mg with an s.c. load, compared to 0.94 (CI 0.45, 1.45) mTSS/year in an untreated patient. Secukinumab showed clinical benefit also in fast progressors; the reduction of their progression rate from 1.46 (0.81, 2.11) to 0.52 (-0.03, 1.04) mTSS/year constitutes a major clinical benefit in this subgroup who previously failed to achieve an adequate response to anti-TNF-α therapy. These patients could be identified and treated with secukinumab in order to prevent progressive and irreversible structural damage leading to mobility and functional limitations (7, 21).

Model fit

The assessment of the model was focused on a pragmatic understanding of fit, rather than ranking competing models using a predefined (*e.g.* information) criterion, since the covariates considered in the model were selected based on the literature and clinical insight. To assess the quality of the model, a question needed to be answered was whether the model had the ability to reproduce the observed mixture distribution of structural damage data, with a large number of patients who

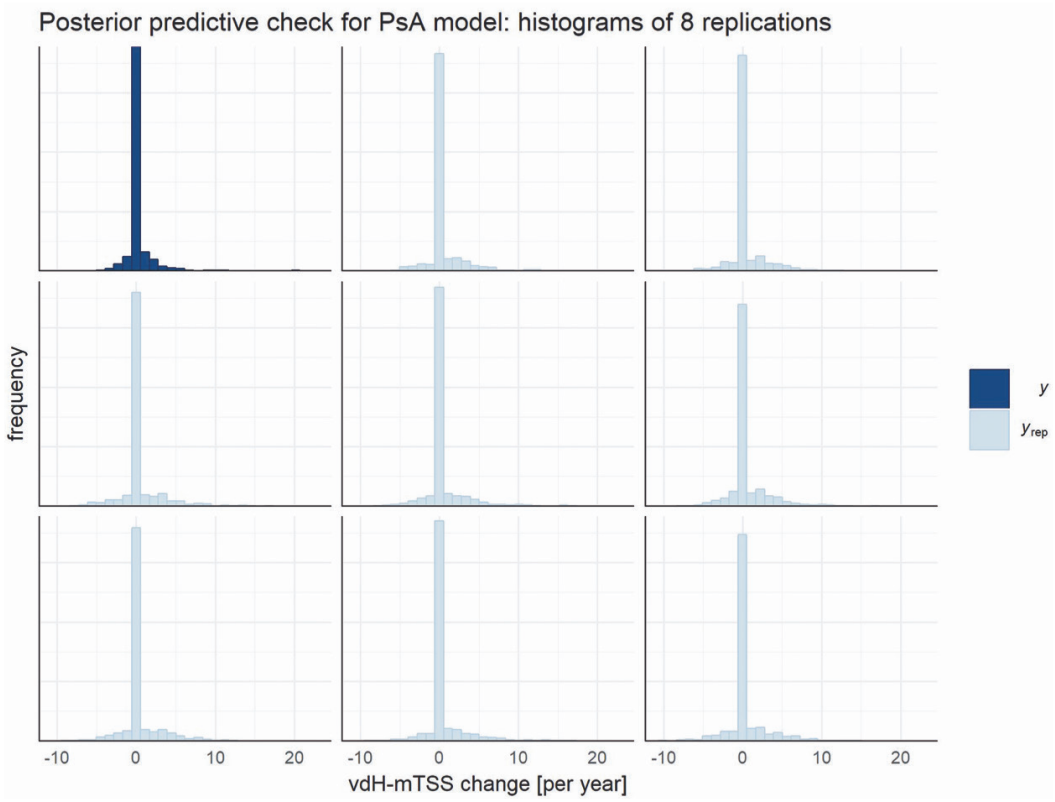

Fig. 2. Model predictive distribution of yearly change in structural damage in PsA *vs*. observed values, shown on a histogram.

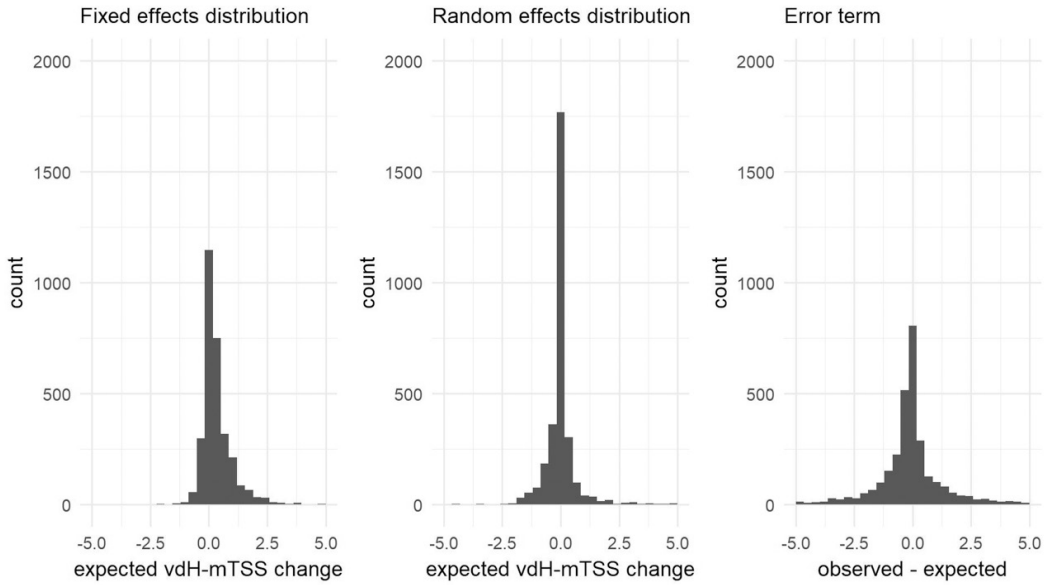

Fig. 3. Histograms for distribution of mean values of modelled measurements from the fixed effects (leftmost panel), estimated random effects (middle panel) and error terms of all modelled measurements (rightmost panel).

do not progress over the duration of the clinical trial. This is presented in Figure 2.

We generate a number of replications to show that the peak at 0 is correctly replicated by the model. Each predictive distribution is based on a single draw from the posterior distribution (approximated with Markov Chain Monte Carlo).

The quality of fit to overall distribution of structural damage is presented in Figure 3. The left panel shows the distribution of expected change in structural damage while taking into account only fixed effects. The middle panel shows the distribution of random effects across patients, and the error term shown on the right is the remaining unexplained difference between the sum of estimated effects (fixed and random) and the measured value.

Strengths of the current study

A strength of our approach is that fact that the model used all available data from all periods of time and all treatment arms to derive information about the risk factors for progression as well as the yearly treatment effect, and exposure-response to secukinumab. We thus do not define a "smallest detectable change" or "smallest detectable difference," an established approach (22) that

reduces the noise in the data at the expense of potentially discarding valuable data. Our analysis further solves difficulties encountered when categorising outcomes to estimate progression. Such difficulties arise from the facts that placebo-controlled results were only available until week 16 or week 24, and that the radiologic assessment is variable. The calculation of proxy exposure to secukinumab allowed us to analyse data of patients coming from all treatment arms and to therefore fully utilise the sample size in spite of the different posologies used in the two available trials, for estimation of the treatment effect and identification of predictors.

Limitations

Our study has several limitations. Placebo data were available only until week 24, which might result in underestimation of the effect of secukinumab. We could only include patients who had at least two measurements of structural damage, which makes our design susceptible to bias due to non-random drop out. The numbers of progressors, and especially of fast progressors, were small, and the RCT population of patients and trial design of the underlying data do not allow assessments of the real-world effect of secukinumab, indicating that these results require additional validation in larger datasets.

Future directions

The next essential step is to apply this model on a robust, longitudinal real-world dataset. The desired features of this dataset include structural damage measured over an extended period of time (years) and assessment of time since diagnosis and time since onset of symptoms to enable better capture the disease stage. Such a dataset would allow improved identification of predictors and fast progressors and therefore increase the statistical power to investigate the hypothesis that early treatment can slow down the pathogenic process in patients with a high risk of fast progression.

In summary, we applied a new methodology to identify statistically significant predictors of structural damage progression, which could potentially allow identifying fast progressors. Our results in fast progressors suggest that early treatment with secukinumab could change their disease trajectory in terms of structural damage. Additional datasets with longer follow up (*e.g.* large real-world datasets) and more diverse treatment patterns should be used in the future to identify significant drivers of efficacy of biologics on structural outcomes, and to pre-emptively identify patients with high risk for faster progression.

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