Patient clusters identified by machine learning from a pooled analysis of the clinical development programme of secukinumab in psoriatic arthritis, ankylosing spondylitis and psoriatic arthritis with axial manifestations

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Abstract

Objective

To identify patient clusters based on baseline demographics and clinical indicators.

Methods

Pooled baseline demographics and clinical data of secukinumab-treated patients from ten Phase III studies in psoriatic arthritis (PsA; FUTURE 1–5 and MAXIMISE), ankylosing spondylitis (AS; MEASURE 1–4), were analysed by machine learning (ML) algorithms. The longitudinal responses of secukinumab 300 mg versus 150 mg were investigated across the clusters and three clinical indicators of tender joints, swollen joints and enthesitis.

Results

3907 patients were grouped into eight distinct clusters based on patient demographics and baseline clinical characteristics. Patients with PsA and axial manifestations (MAXIMISE) were overrepresented in clusters 6–8. Patients in cluster 6 (mean age 48 years; 46% male) were overweight with pronounced psoriasis, higher articular burden in knees, shoulders, elbows and wrists. Patients in cluster 7 (mean age 47 years; 53% male) were less overweight with lower polyarticular joint counts and tenderness of the joints of the feet, wrists and hands. Patients in cluster 8 were predominantly with AS (mean age 43 years; 64% male) with a mean body mass index of 27.3 kg/m^2, oligoarthritis and high prevalence of spinal pain. Patients with PsA (FUTURE) were overrepresented in clusters 1–5. Longitudinal analysis showed improvements with secukinumab 300 mg versus 150 mg in clusters 6 and 8 for tender joint counts, and cluster 7 for swollen joint counts.

Conclusion

PsA clusters obtained by ML in pooled dataset indicate phenotypical heterogeneity of patients with PsA and axial manifestations and overlapping features across the spondyloarthritis spectrum.

Key words

ankylosing spondylitis, machine learning, psoriatic arthritis, spondyloarthritis

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory, heterogenous, musculoskeletal disease that can affect peripheral joints and the axial skeleton (1, 2). The prevalence of axial disease in patients with PsA varies with disease duration and the definition used, occurring in 25–70% of patients with longstanding PsA (3). Currently, there are neither universally accepted classification criteria nor any consensus on the definition for axial PsA (1). A prospective cross-sectional study on axial involvement in patients with PsA (AXIS) was recently initiated to evaluate clinical and imaging manifestations indicative of axial involvement in patients with PsA and to develop classification criteria for axial PsA (4).

Machine learning (ML) techniques can investigate patterns from large clinical datasets and identify distinct clusters of patients with potential therapeutic or prognostic significance, leading to a better understanding of the disease and evolution towards precision medicine (5). ML can deal with complex, non-linear relationships between patient attributes which are difficult to model with statistical methodologies and hence, support the development of models predicting responses to treatments and disease progression (6). The potential of ML to identify distinct clusters of patients with potential therapeutic or prognostic significance has been demonstrated in a pooled analysis of four Phase III trials in patients with PsA (FUTURE 2–5) (5).

The aim of this *post-hoc* analysis was to identify distinct clinical clusters based on patient demographics and baseline clinical indicators from the clinical development programme of secukinumab in patients with PsA, ankylosing spondylitis (AS), and PsA with axial manifestations and further support the characterisation of the axial PsA phenotype within the spondyloarthritis (SpA) spectrum.

Methods

Data description

Pooled clinical data at baseline from patients with PsA, AS or axial PsA treated with secukinumab across ten Phase III studies, namely, FUTURE 1–5 (PsA) (7-11), MEASURE 1–4 (AS) (12-14) and MAXIMISE (axial PsA) (15) were analysed.

Cluster analysis

Patient demographics (sex, age, body mass index [BMI]), disease characteristics and clinical indicators of the PsA manifestations including swollen and tender joints, Achilles tendon enthesitis, presence of dactylitis, psoriasis (PsO), C-reactive protein (CRP, >5 mg/L) and spinal pain were analysed to identify clusters of patients using ML algorithms. Achilles tendon enthesitis was evaluated clinically by the investigator. The assessment of spinal pain varied across the FUTURE, MAXIMISE and MEASURE development programmes in terms of use of the 100 mm visual analogue scale (VAS) in assessing the level of pain and the collection of parameters indicating the inflammatory nature of back pain. Finite mixture model methodology was applied to the pooled clinical data of secukinumab-treated patients from ten clinical trials (FUTURE, MEASURE and MAXIMISE).

The underlying assumption of the model was "if two patients belong to the same cluster then their clinical measurements (across the 84 binary variables) share similar multinomial distribution". The clustering algorithm was applied repeatedly on different subsamples of the patients to assess clustering robustness and stability.

Longitudinal analysis

The longitudinal responses across the identified clusters, and the three clinical indicators, namely tender joints, swollen joints and enthesitis, were explored for the two doses of secukinumab, 150 and 300 mg. Furthermore, curves depicting relative mean and the difference between the relative mean to secukinumab 150 mg response and secukinumab 300 mg response were generated for each cluster and endpoint. The relative mean of each endpoint at time t was defined as the endpoint mean at time t divided by the endpoint mean at baseline. The bootstrap confidence intervals used an alpha=0.05 and were

Table I. Summary statistics and trial tabulation by cluster.

		PsO (+)	PsO (+)	ACH (-)	ACH (+) PsO (++)	M-TEN DAC (-)	ACH (-) DAC (-) PsO (-)
Variables, n (%) unless otherwise specified	Cluster 1 (n=567)	Cluster 2 (n=420)	Cluster 3 (n=164)	Cluster 4 (n=452)	Cluster 5 (n=403)	Cluster 6 (n=408)	Cluster 7 (n=193)	Cluster 8 (n=1300)
Patient demographics								
Male	225 (39.7)	183 (43.6)	98 (59.8)	193 (42.7)	239 (59.3)	187 (45.8)	103 (53.4)	829 (63.8)
BMI (kg/m^2), mean (SD)	30.04 (7.05)	29.63 (6.53)	28.45 (5.40)	30.25 (6.68)	28.11 (5.39)	30.17 (6.15)	28.63 (5.09)	27.28 (5.41)
Age (years), mean (SD)	51.26 (11.58)	47.78 (12.01)	46.54 (11.59)	49.89 (11.93)	48.35 (12.20)	48.17 (12.22)	46.93 (11.67)	42.90 (12.14)
Disease characteristics and clinical indicators								
SJC, mean (SD)	14.62 (8.44)	7.21 (4.49)	3.98 (1.93)	8.82 (4.00)	5.45 (2.80)	5.03 (2.43)	3.73 (2.78)	0.92 (1.30)
TJC, mean (SD)	28.96 (7.22)	16.02 (4.87)	7.15 (2.67)	15.07 (4.48)	7.46 (3.21)	8.56 (2.76)	10.93 (3.12)	2.52 (2.40)
Achilles tendon*, mean (SD)	1.01 (0.91)	0.87 (0.90)	0.37 (0.66)	0.45 (0.76)	0.24 (0.57)	0.72 (0.88)	0.48 (0.75)	0.29 (0.64)
Dactylitis presence	247 (43.6)	156 (37.1)	76 (46.3)	171 (37.8)	139 (34.5)	150 (36.8)	48 (24.9)	206 (15.9)
Psoriasis presence	254 (44.9)	185 (44.0)	85 (51.8)	233 (51.5)	197 (48.9)	252 (61.8)	84 (43.5)	410 (31.5)
CRP >5 mg/L	278 (49.0)	213 (50.7)	71 (43.3)	227 (50.2)	155 (38.5)	228 (55.9)	86 (44.6)	665 (51.2)
Spinal pain presence#	184 (32.5)	176 (41.9)	62 (37.8)	138 (30.5)	100 (24.8)	162 (39.7)	104 (53.9)	1035 (79.6)
Development programme	**Total**							
FUTURE	2453 (62.78)	493 (86.95)	323 (76.9)	130 (79.27)	386 (85.4)	354 (87.84)	303 (74.26)	121 (62.69)	343 (26.38)
MAXIMISE	485 (12.41)	45 (7.94)	43 (10.24)	19 (11.59)	45 (9.96)	29 (7.20)	65 (15.93)	40 (20.73)	199 (15.31)
MEASURE	969 (24.8)	29 (5.11)	54 (12.86)	15 (9.15)	21 (4.65)	20 (4.96)	40 (9.8)	32 (16.58)	758 (58.31)

*Presence of Achilles tendon enthesitis for the right or left foot. #Presence of back pain.
Dark red signifies highest proportion of females who are older in age and have moderate-high polyarticular burden (swollen/tender joints). Yellow signifies high proportion of females who are comparatively younger in age and have moderate-low polyarticular burden. Dark blue represents high proportion of males who are older in age and have low polyarticular burden. Light blue represents the highest proportion of males who are comparatively younger in age and have very low polyarticular burden.
ACH: Achilles; BMI: body mass index; CRP: C-reactive protein; DAC: dactylitis; H: high; L: low; M: medium; n: number of evaluable patients; PsO: psoriasis, SD: standard deviation; SJC: swollen joint counts; SWO: swollen; TEN: tender; TJC: tender joint counts; VL: very low

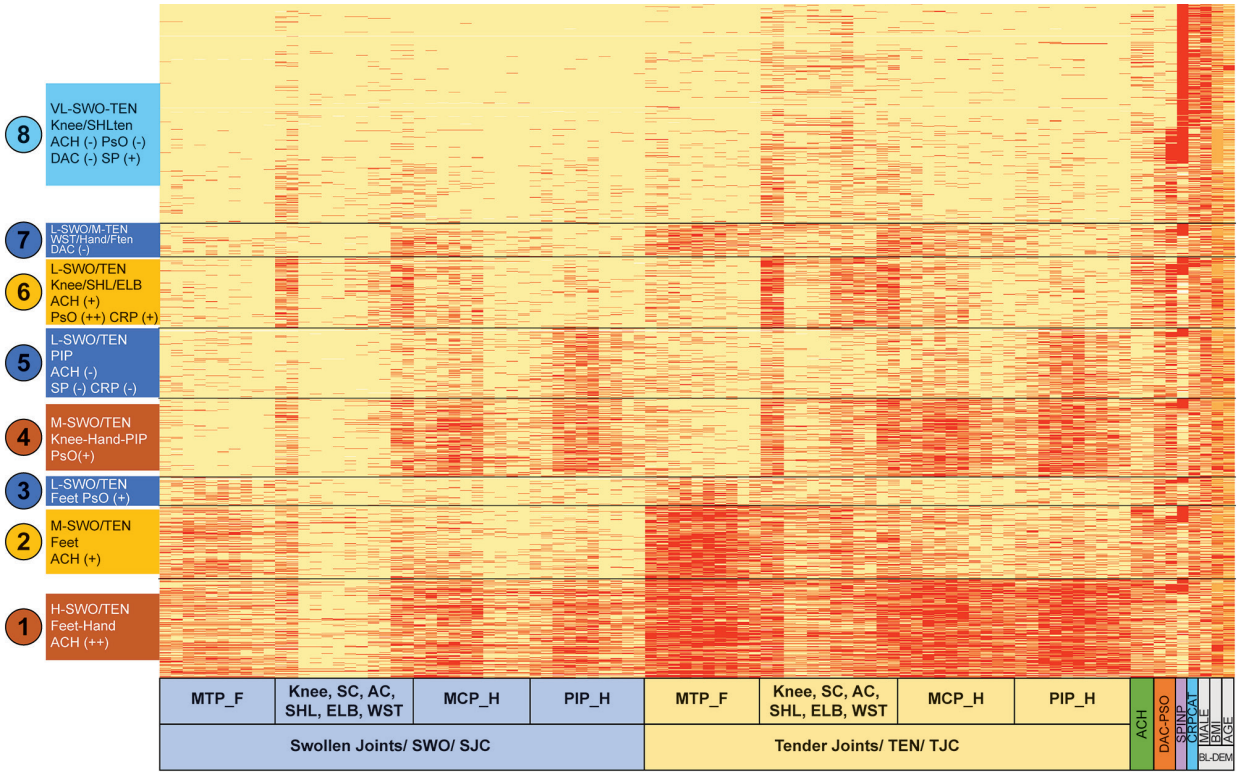

Fig. 1. Heat map of baseline clusters from the FUTURE, MEASURE and MAXIMISE studies.
Dark red signifies highest proportion of females who are older in age and have moderate-high polyarticular burden (swollen/tender joints). Yellow signifies high proportion of females who are comparatively younger in age and have moderate-low polyarticular burden. Dark blue represents high proportion of males who are older in age and have low polyarticular burden. Light blue represents the highest proportion of males who are comparatively younger in age and have very low polyarticular burden. AC: acromioclavicular; ACH: Achilles; BL-DEM: baseline demographics; Aver: average; BMI: body mass index; CRPCAT: C-reactive protein (categorical); DAC: dactylitis; ELB: elbow; Ften: feet tenderness; H: high; L: low; M: medium; MCP_H: metacarpophalangeal joints hand; MTP_F: metatarsophalangeal joint feet; PIP_H: proximal interphalangeal joints hand; PSO: psoriasis: SC: sternoclavicular; SHL: shoulder; SHLten: shoulder tenderness; SPINP/SP: spinal pain; SWO: swollen; TEN: tender; VL: very low; WST: wrist

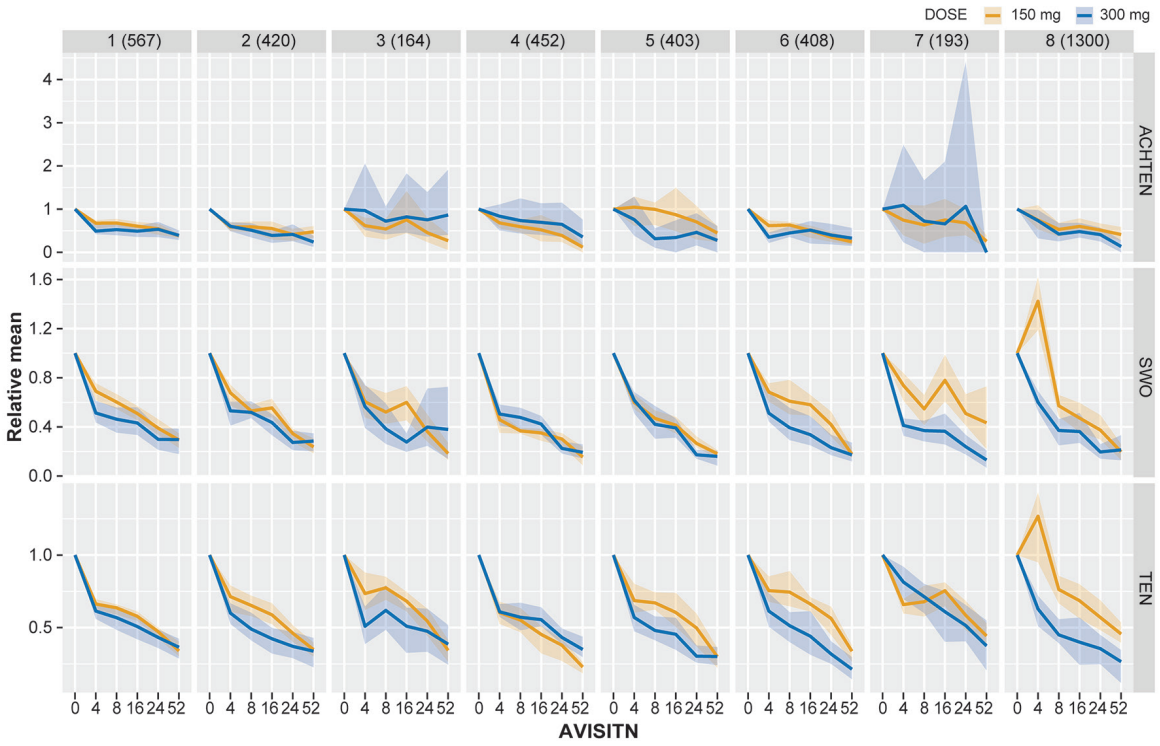

Fig. 2A. Bootstrap (relative) treatment means with Bonferroni adjusted 95% bootstrap intervals by cluster.
The orange and blue curves depict the relative mean responses for patients having received secukinumab 150 mg and secukinumab 300 mg, respectively. The two relative dose-response curves always started at baseline at the same mean value equal to 1 to adjust for different starting values. The coloured shaded regions represent the corresponding Bonferroni adjusted 95% bootstrap CIs.
ACHTEN: Achilles tendon; AVISTN: analysis visit number; CI: confidence interval; SWO: swollen; TEN: tender.

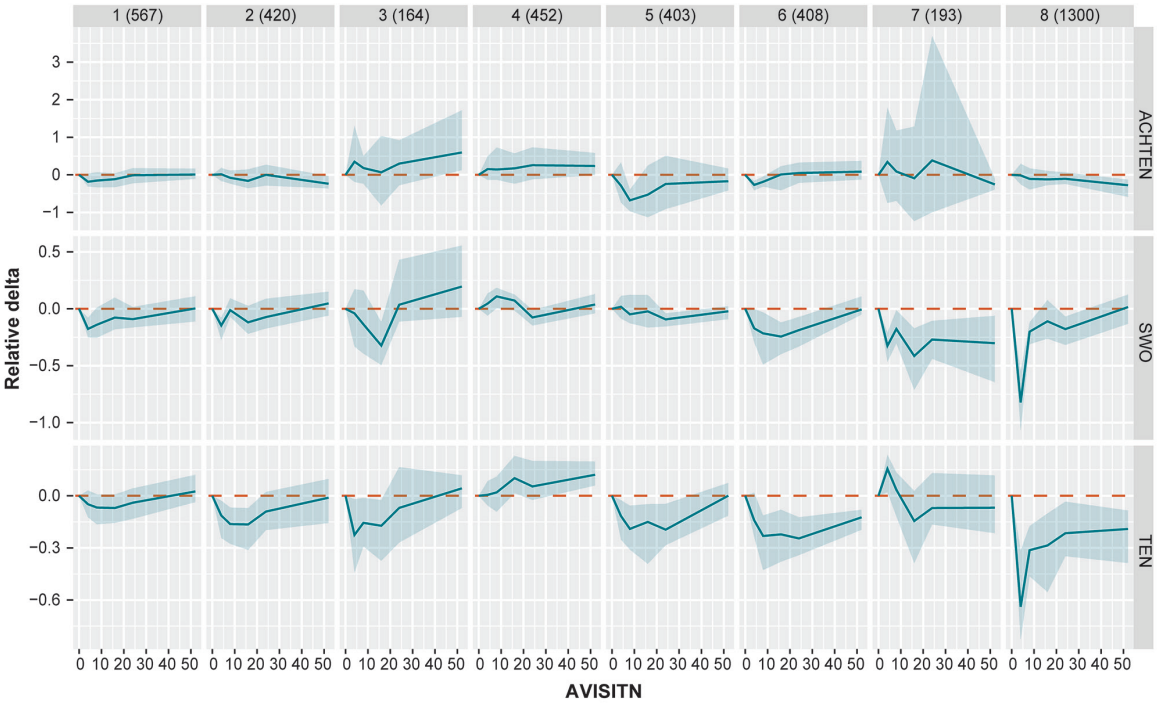

Fig. 2B. Bootstrap (relative) treatment difference ([300 mg]–[150 mg]) with Bonferroni adjusted 95% bootstrap intervals by cluster.
The codes used for the analysis did not consider the study visit weeks (week 0, 4, 8, 16, 24, 54) as the time intervals between visits were not the same. The curves pass through zero at baseline to ensure that the observed treatment differences are not due to the two patient populations starting from a different baseline disease activity. The coloured shaded regions represent the corresponding Bonferroni adjusted 95% bootstrap CIs. If the shaded region excluded the zero line (the red dashed line), then the longitudinal treatment difference between secukinumab 300 and 150 mg is deemed statistically significant.
ACHTEN: Achilles tendon; AVISTN: analysis visit number; CI: confidence interval; SWO: swollen; TEN: tender.

further adjusted using Bonferroni correction, which considers 24 comparisons at the same time (three endpoints × eight clusters). Curves depicting the difference between the relative mean responses to secukinumab 300 mg and secukinumab 150 mg across the eight clusters for each of the three clinical indicators were also generated.

Results

Of 3907 patients who were included in the analysis, 2453 patients (62.8%) were enrolled in the FUTURE studies, 969 (24.8%) in the MEASURE studies and 485 (12.4%) in the MAXIMISE study (Table I). Patients' demographics and baseline clinical characteristics by clusters are detailed in Table I.

Cluster analysis

Figure 1 shows the heat map of baseline clusters from the FUTURE, MEASURE and MAXIMISE studies, wherein each row corresponds to one patient and each column corresponds to one clinical variable. In total, eight distinct patient clusters were identified based on the demographics and baseline disease manifestations. Patients with PsA and axial manifestations from the MAXIMISE trial were overrepresented in clusters 6–8 (Table I). Patients in cluster 6 (mean age of 48 years; 46% male) were overweight (mean BMI 30.2 kg/m^2) with pronounced psoriasis (PsO), and high articular burden of the knees, shoulders, elbows, and wrists. Patients in cluster 7 (mean age of 47 years; 53% male) were less overweight (mean BMI 28.6 kg/m^2) with low polyarticular joint counts and tenderness focused on the feet, wrists and hands. Patients with AS were overrepresented in cluster 8 (mean age of 43 years; 64% male) with a mean BMI of 27.3 kg/m^2, having oligoarthritis and high prevalence of spinal pain.

Patients with PsA from the FUTURE studies were overrepresented in clusters 1–5 (Table I, Fig. 1). Cluster 1 was predominantly a PsA cluster of older female patients, having high BMI (30 kg/m^2), with polyarticular burden and Achilles tendon enthesitis. Baseline characteristics were consistent in clusters 2 and 4 (mean age 48 and 50 years; 44% and 43% male; mean BMI 29.6 kg/m^2 and 30.3 kg/m^2, respectively; Table I); however, cluster 2 was primarily characterised by medium articular burden of the feet and knees and the presence of Achilles tendon enthesitis, whereas cluster 4 was characterised by medium articular burden of the hands and wrists and high prevalence of PsO. Baseline characteristics of patients in clusters 3 and 5 were also similar (Table I), except that cluster 3 was marked by articular burden of the feet and knees and presence of PsO and cluster 5 was marked by notable swelling and tenderness of the hands and low Achilles tendon enthesitis.

Longitudinal response

A visual comparison of the two mean longitudinal response curves for secukinumab 300 mg and secukinumab 150 mg across the eight identified clusters and three clinical indicators is shown in Figure 2A. The curves depicting the difference between the relative mean responses to secukinumab 300 mg and secukinumab 150 mg across the eight clusters for each of the three clinical indicators are shown in Figure 2B. Significantly higher improvements in the secukinumab 300 mg group compared with the secukinumab 150 mg group were shown in cluster 6 and cluster 8 for tender joint counts (TJC), and in cluster 7 for swollen joint counts (SJC; Fig. 2B).

Discussion and conclusion

In this *post-hoc* ML analysis of the pooled dataset of the FUTURE, MEASURE, and MAXIMISE trials, eight clusters were identified. Although the demographics and baseline disease characteristics displayed pattern similarities, the clusters were distinct with variable representation from the population of the pooled trials. Patients with PsA and axial manifestations in particular, were phenotypically heterogeneous with overlapping features across the SpA spectrum. Furthermore, longitudinal analysis showed improved responses in TJC and SJC with secukinumab 300 mg compared with secukinumab 150 mg for some clusters, suggesting that the clustering effort may also have predictive value in terms of differential treatment effect of the two secukinumab doses.

The main limitation of the current *post-hoc* analysis stems from the different data collection requirements across the FUTURE, MEASURE and MAXIMISE programmes, which restricts the clustering to the commonly collected clinical indicators and limits the longitudinal analyses to six visits and only three clinical indicators. Therefore, further studies are needed to refine or validate these clusters and the differences in response to therapy to eventually determine distinct phenotypes across the SpA spectrum. Although the primary focus of this *post-hoc* analysis was to explore the axial PsA phenotype, MAXIMISE represented the smallest group (12.4%) of the pooled population.

Despite these limitations, the current *post-hoc* analysis further corroborates the value of ML in analysing large datasets and highlights overlapping clinical features across the SpA spectrum. More importantly, it indicates the phenotypical heterogeneity of patients with PsA and axial manifestations and is shedding light on the characterisation of axial PsA.

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Competing interests

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