

Defining trajectories of response in patients with psoriasis treated with biologic therapies

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Summary

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Conflicts of interest

Conflicts of interest statements can be found in the Appendix.

Data availability

The data that support the findings of this study are available from BADBIR (<http://www.badbir.org/> and ClinicalStudyDataRequest.com). Restrictions apply to the availability of these data, which were used under license for this study.

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Background The effectiveness and cost-effectiveness of biologic therapies for psoriasis are significantly compromised by variable treatment responses. Thus, more precise management of psoriasis is needed.

Objectives To identify subgroups of patients with psoriasis treated with biologic therapies, based on changes in their disease activity over time, that may better inform patient management.

Methods We applied latent class mixed modelling to identify trajectory-based patient subgroups from longitudinal, routine clinical data on disease severity, as measured by the Psoriasis Area and Severity Index (PASI), from 3546 patients in the British Association of Dermatologists Biologics and Immunomodulators Register, as well as in an independent cohort of 2889 patients pooled across four clinical trials.

Results We discovered four discrete classes of global response trajectories, each characterized in terms of time to response, size of effect and relapse. Each class was associated with differing clinical characteristics, e.g. body mass index, baseline PASI and prevalence of different manifestations. The results were verified in a second cohort of clinical trial participants, where similar trajectories following the initiation of biologic therapy were identified. Further, we found differential associations of the genetic marker HLA-C*06:02 between our registry-identified trajectories.

Conclusions These subgroups, defined by change in disease over time, may be indicative of distinct endotypes driven by different biological mechanisms and may help inform the management of patients with psoriasis. Future work will aim to further delineate these mechanisms by extensively characterizing the subgroups with additional molecular and pharmacological data.

What is already known about this topic?

- While many patients with psoriasis respond to treatment with biologics, there are those who show little or no response and those who respond initially but then either lose response or suffer from adverse effects.

- Better characterization of patients who will, or will not, benefit from biologic therapy will facilitate the understanding of relevant biological mechanisms and explain treatment outcome variation in patient cohorts.

What does this study add?

- Using a data-driven approach, we identified four subgroups of patients with psoriasis defined by global trajectories of response to biologic therapies.
- Our results were replicated in a second cohort obtained by pooling data from four clinical trials of biologic therapies for psoriasis.
- We further identified potential human leucocyte antigen biomarkers that help to distinguish between the trajectory-based subgroups.

Biologic therapies have revolutionized outcomes for people with severe psoriasis. However, these drugs are expensive and while many patients respond well to treatment there are subgroups who are considered 'primary failures' or secondary (responding initially but then losing response) failures, or who suffer adverse effects.^{1,2} A recent network meta-analysis of 41 randomized controlled trials indicated significant heterogeneity in response between biologics for psoriasis with respect to effectiveness and tolerability;³ however, traditional methods used to understand this heterogeneity in response have largely been uninformative.^{4–6}

Relatively little attention has been paid to the trajectories of disease progression and treatment response, which may differ greatly between patients. For example, the examination of response trajectories to clozapine in a secondary analysis of pivotal trials has supported the use of treatment-response trajectories to subtype patients with schizophrenia;⁷ and a simple post hoc analysis of methotrexate trial data hints at subtypes of response in psoriasis with the description of 'early' and 'late' responders.⁸

With the vision of the Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium being to further personalized medicine in psoriasis by gaining a better understanding of the global patterns of disease,⁹ we took a data-driven approach with an unsupervised statistical learning method to identify latent classes, or subgroups, of patients with psoriasis that display similar patterns of disease severity over time (i.e. trajectories) following biologic treatment. Latent class mixed modelling (LCMM) has previously been successful in the identification of patterns of predisease obesity in type 2 diabetes.¹⁰ Here, we applied latent class trajectory analysis to analyse a large-scale, longitudinal, patient-level, real-world, cohort – the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) – to test (i) whether we could identify universal subgroups of patients with psoriasis with distinct patterns of change in disease following the initiation of biologic therapies; (ii) assess baseline characteristics and differences between identified subgroups; (iii) identify differential risk of treatment failure that is

associated with the identified trajectory subgroups; and (iv) determine the association of any identified subgroups with a known genetic marker (HLA-C*06:02). We validated this approach by identifying similar trajectory-based subgroups in a second, independent cohort of patients with psoriasis treated with biologic therapies in clinical trials.

Materials and methods

British Association of Dermatologists Biologics and Immunomodulators Register participants and data

All data were obtained from BADBIR,¹¹ which is a large prospective observational register of adults with psoriasis treated with either biologic therapies or nonbiological systemic therapies. It was established with the aim of evaluating the long-term, real-world safety of biologics in the treatment of psoriasis. Following registration and acquisition of baseline data, changes in therapy, disease activity and adverse events are recorded for each patient (6-monthly for 3 years, then annually).

Of 10 638 registered patients with psoriasis from 152 dermatology departments in the UK and Ireland, in the period of March 2007–August 2015, 3546 fulfilled the inclusion criteria. These were patients (i) receiving their first biologic therapy [including the tumour necrosis factor (TNF) inhibitors adalimumab, etanercept and infliximab, and the interleukin (IL)-12/IL-23 inhibitor ustekinumab; Table 1 and Figure 1]; (ii) with a baseline Psoriasis and Area Severity Index (PASI) measurement ≥ 10 , signifying moderate-to-severe psoriasis; and (iii) with complete baseline data (no minimal follow-up required). A total of 12 751 observations (PASI) were included (7429 adalimumab; 2938 etanercept; 264 infliximab; and 2120 ustekinumab). The number of PASI measurements per patient ranged from 1 to 17, with a mean (SD) of 3.6 (2.5); and a mean (SD) follow-up of 1.2 (1.0) years (interquartile range 0–2.1) – these were sufficient to derive response trajectories using LCMMs.

Table 1 Baseline characteristics, and 75% reduction in Psoriasis Area and Severity Index (PASI 75) and 90% reduction in PASI (PASI 90) response of patients in the entire cohort and in each of the four resulting latent classes (in the four-class model)

	Entire cohort	Class 1	Class 2	Class 3	Class 4	P-value	Bonferroni
Patients (n)	3546	386 (10.9)	238 (6.7)	943 (26.6)	1979 (55.8)	–	
Mean (SD) duration of follow-up (years)	1.2 (1.0)	1.2 (0.8)	2.0 (0.8)	1.5 (0.8)	0.9 (1.1)	< 0.001	
Mean (SD) age at baseline (years)	45.1 (12.7)	45.8 (12.6)	45.8 (12.6)	45.0 (12.3)	45.0 (13.0)	0.527	
Mean (SD) age at diagnosis (years)	23.5 (13.1)	23.9 (13.3)	23.0 (13.1)	23.5 (12.7)	23.5 (13.3)	0.863	
Sex						0.09	
Female	1410 (39.8)	151 (39.1)	103 (43.3)	345 (36.6)	811 (41.0)		
Male	2136 (60.2)	235 (60.9)	135 (56.7)	598 (63.4)	1168 (59.0)		
Mean (SD) BMI (kg m ⁻²)	31.1 (7.2)	32.7 (7.5)	31.1 (7.0)	31.3 (7.4)	30.7 (7.0)	< 0.001	< 0.001
BMI subcategory						< 0.005	< 0.05
Underweight (BMI < 18.5)	34 (1.0)	3 (0.8)	1 (0.4)	9 (0.9)	21 (1.1)		
Normal weight (BMI 18.5–24.9)	595 (16.8)	44 (11.4)	39 (16.4)	160 (17.0)	352 (17.8)		
Overweight (BMI 25.0–29.9)	1131 (31.9)	109 (28.2)	80 (33.6)	288 (30.5)	654 (33.0)		
Obese class I (BMI 30.0–34.9)	920 (25.9)	101 (26.2)	63 (26.5)	233 (24.7)	523 (26.4)		
Obese class II (BMI 35.0–39.9)	487 (13.7)	72 (18.6)	28 (11.8)	150 (15.9)	237 (12.0)		
Obese class III (BMI ≥ 40)	379 (10.7)	57 (14.8)	27 (11.3)	103 (10.9)	192 (9.7)		
Ethnicity						0.518	
Asian	165 (4.6)	22 (5.7)	9 (3.8)	42 (4.5)	92 (4.6)		
Black	19 (0.5)	3 (0.8)	1 (0.4)	3 (0.3)	12 (0.6)		
White	3246 (91.5)	346 (89.6)	219 (92.0)	868 (92.0)	1813 (91.6)		
Other	116 (3.3)	15 (3.9)	9 (3.8)	30 (3.2)	62 (3.1)		
Drug						< 0.001	< 0.001
Adalimumab	2088 (58.9)	191 (49.5)	149 (62.6)	488 (51.7)	1260 (63.7)		
Etanercept	830 (23.4)	142 (36.8)	35 (14.7)	294 (31.2)	359 (18.1)		
Infliximab	68 (1.9)	8 (2.1)	4 (1.7)	16 (1.7)	40 (2.0)		
Ustekinumab	560 (15.8)	45 (11.7)	50 (21.0)	145 (15.4)	320 (16.2)		
Smoking						0.227	
Current smoker	972 (27.4)	111 (28.8)	68 (28.6)	244 (25.9)	549 (27.7)		
Past smoker	1071 (30.2)	105 (27.2)	75 (31.5)	301 (31.9)	590 (29.8)		
Never smoked	999 (28.2)	94 (24.4)	62 (26.1)	244 (25.9)	599 (30.3)		
NA	504 (14.2)	76 (19.7)	33 (13.9)	154 (16.3)	241 (12.2)		
Psoriasis type							
Erythrodermic	225 (6.3)	43 (11.1)	7 (2.9)	51 (5.4)	124 (6.3)	< 0.001	0.003
Flexural	1434 (40.4)	168 (43.5)	136 (57.1)	577 (61.2)	1181 (59.7)	0.369	
Guttate	507 (14.3)	60 (15.5)	33 (13.9)	129 (13.7)	285 (14.4)	0.841	
Seborrhoeic	629 (17.7)	78 (20.2)	29 (12.2)	171 (18.1)	351 (17.7)	0.081	
Involved areas							
Nails	2049 (57.8)	234 (60.6)	144 (60.5)	577 (61.2)	1094 (55.3)	0.009	0.290 ^a
Palms/soles	731 (20.6)	109 (28.2)	43 (18.1)	198 (21.0)	381 (19.2)	< 0.001	0.023
Scalp	2601 (73.3)	298 (77.2)	169 (71.0)	689 (73.1)	1445 (73.0)	0.290	
Past UV exposure	2679 (75.5)	305 (79.0)	186 (78.2)	721 (76.5)	512 (25.9)	0.113	
Mean (SD) baseline PASI	17.9 (7.7)	22.3 (9.5)	17.3 (7.3)	16.9 (6.7)	17.7 (7.5)	< 0.001	< 0.001
Mean (SD) PASI 75 at 4–8 months ^b	1270 (67.6)	34 (13.4)	108 (69.2)	413 (68.6)	715 (83.5)	< 0.001	< 0.001
Mean (SD) PASI 90 at 4–8 months ^b	819 (43.6)	7 (2.7)	39 (25.0)	142 (23.6)	631 (73.7)	< 0.001	< 0.001

Data are n (%) unless otherwise stated. BMI, body mass index; NA, not available; UV, ultraviolet. ^aNot statistically significant after Bonferroni adjustment of the P-value. ^bOf those with available data.

Latent class mixed models

LCMM is a type of latent class analysis that identifies unmeasured class membership among subjects using observed categorical and/or continuous variables, and includes a random intercept and random coefficients for each individual; it is used to identify meaningful subgroups with homogeneous pattern of change over time.

In this study, we specified LCMMs with PASI as the dependent/outcome variable. Mixed effects were used to account

for the likely correlation of repeated measurements within the same patient and included a random intercept for each individual. In all the models, we assumed the effects of included potential confounders to be the same for all latent classes and aimed to identify latent classes with different regression parameters vs. time.

In each case, we tested the model for 1–10 latent classes and the optimal number of latent classes was assessed using the Bayesian Information Criterion (BIC); the model with the lowest BIC and at least 5% of patients in all the resulting

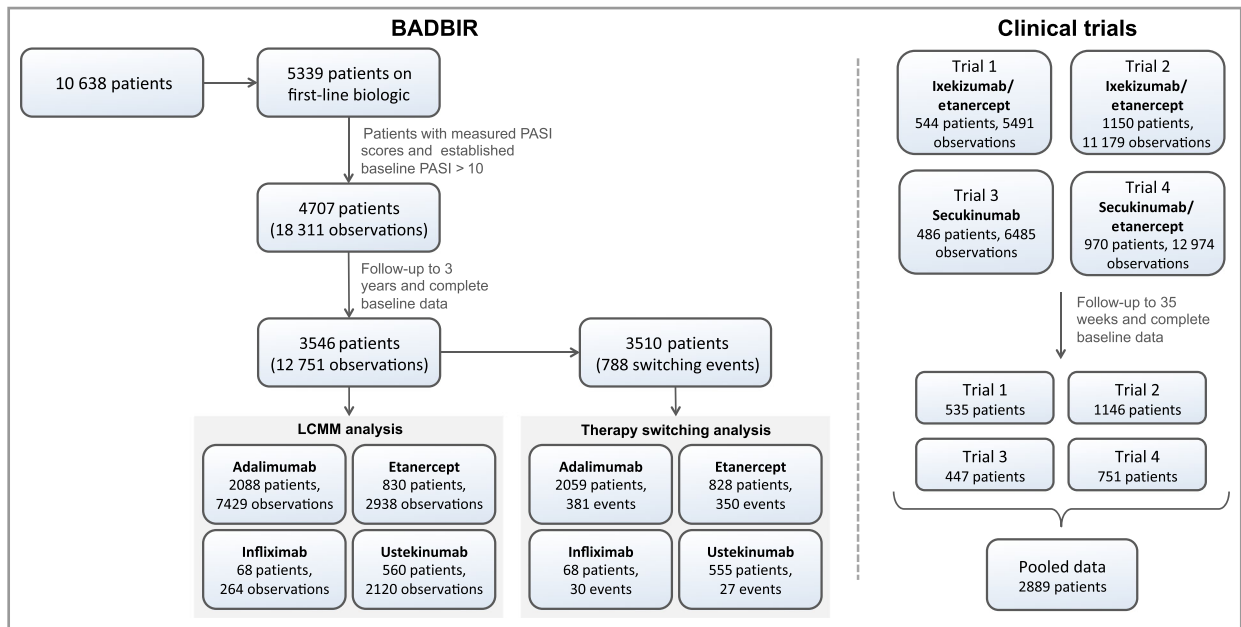


Figure 1 Schematic of cohort selection for the latent class mixed modelling (LCMM) and therapy switching analyses. BADBIR, British Association of Dermatologists Biologics and Immunomodulators Register; PASI, Psoriasis Area and Severity Index.

classes, was selected (Figure S1; see Supporting Information). At model convergence, each patient was assigned exclusively to the class for which the highest posterior probability was obtained. This class assignment was used for the subsequent characterization of the classes.

Identification of subgroups of response to biologics

We used a LCMM, applied to the BADBIR dataset, with the aim of identifying subgroups of patients with distinct patterns of disease over time, as measured by PASI. Patient-level variables were then used to define the distinguishing characteristics of the subgroups. Full details of the model specifications and statistical analyses can be found in Appendix S2 and Figure S1 (see Supporting Information). All analyses were computed using R version 3.2.3.¹² Results are presented as the main effect with a 95% confidence interval (CI) where possible. A significance threshold of 5% was used for main inferences.

Sensitivity analysis in patients treated with adalimumab

A further LCMM analysis was carried out on a subset of data from adalimumab-treated patients within BADBIR. This included 2,088 patients with a total of 7,429 observations (PASI measurements; Figure 1). The model was specified as described above and the best-fit model was selected using the same criteria.

Latent class analysis in clinical trial data

Access to data from four randomized, placebo-controlled trials evaluating biologics (etanercept, secukinumab and ixekizumab) in chronic plaque psoriasis was requested, approved by ClinicalStudyDataRequest.com (application ID: 1693) and

obtained through the Clinical Trial Data Transparency programme (April 2018). The four trials are NCT01597245, NCT01646177, NCT01365455 and NCT01358578 (full details in Appendix S2), and were selected for their availability of data through the ClinicalStudyDataRequest.com platform.

We applied an LCMM to data from 2,889 patients pooled from these four clinical trials in order to identify global trajectories of PASI over time, matching the analysis parameters to those in the analysis of data from BADBIR. Full details of this analysis can be found in Appendix S2.

A second analysis, to verify the reproducibility and consistency of the latent class model identified in the BADBIR registry data, was also carried out. Here, patients from the clinical trials cohort were assigned to one of the four classes identified in BADBIR using PASI measures at 3 and 6 months, and their trajectories were plotted and visually compared with those obtained in the BADBIR data (full details can be found in Appendix S2).

Human leucocyte antigen analysis

Data on HLA-C*06:02 status (i.e. the copy number of this allele) were available for a subset of BADBIR participants enrolled in the associated Biomarkers of Systemic Treatment Outcomes in Psoriasis (BSTOP) study (<https://bit.do/BSTOP>). Using these data on 1,209 individuals, we examined associations of this biomarker with the trajectory classes identified in BADBIR.^{13,14} Full details of this analysis are available in Appendix S2.

Ethics approvals

This study was conducted in accordance with the principles of the 2008 Declaration of Helsinki. Samples and data were provided through the PSORT Discovery [PSORTD; approved by

National Research Ethics Service Committee London – London Bridge (ethics approval code 14/LO/1685)], which is nested within the BSTOP study (approved by National Research Ethics Service Committee London – South East2; ethics approval code 11/H0802/7). Written informed consent was obtained from all participants before enrollment.

Results

Latent class analysis identified four distinct subtypes of response trajectory

Data on 3546 patients from BADBIR who fulfilled our inclusion criteria were used to identify subgroups of patients with similar PASI trajectories over time.¹¹ These were patients receiving their first biologic therapy (including the TNF inhibitors adalimumab, etanercept and infliximab, and the IL-12/IL-23 inhibitor ustekinumab; Table 1 and Figure 1). We applied a LCMM and, based on the lowest BIC while requiring at least 5% of patients in all resulting classes (Figure S1),¹⁵ identified four trajectory latent classes following the initiation of any first-line biologic therapy in patients with psoriasis: 10.9% in class 1; 6.7% in class 2; 26.6% in class 3; and 55.8% in class 4. On average, all classes showed some reduction in disease severity. However, while classes 1 and 3 demonstrated a moderate but sustained reduction over time, classes 2 and 4 demonstrated an increase in disease severity following an initial reduction (Figure 2). Notably, the proportion of responders to therapy differed between the classes with a much lower rate of those with a 75% or greater reduction in PASI score (PASI 75) in class 1 (13.4%) vs. class 4 (83.5%;

Table 1). Classes 2 and 3 demonstrated similar rates of PASI 75 (69.2% and 68.6%, respectively; Table 1). This finding was consistent for a 90% or greater reduction in PASI score (PASI 90) outcomes at 4–8 months (Table 1). To evaluate whether these results were driven by the differential relative effectiveness of the specific biologic therapies, a LCMM analysis was conducted on the adalimumab-treated group alone, the only single drug for which sufficient data were available. This resulted in a good fit of the same four-class model (Figure S2; see Supporting Information), suggesting that the identified subtypes were generic rather than treatment specific. Nevertheless, we could not rule out that responses to different drugs would yield different trajectories.

Differences were found between the four resulting classes in body mass index (BMI), baseline PASI and the specific biologic therapies that patients were receiving ($P < 0.001$; Table 1). For example, class 1 demonstrated a higher proportion of patients with erythrodermic psoriasis ($P = 0.003$) and/or involvement of the palms/soles ($P = 0.023$) than the other classes.

To determine whether any of the identified classes were associated with differential risk of treatment failure, we examined the time to switching (i.e. from first-line biologic to a second line of therapy) or ending therapy in each of the resulting subgroups. This unadjusted analysis revealed that class 2 demonstrated the overall lowest rates of switching, while class 1 demonstrated the highest rates of switching [hazard ratio (HR) 0.15 (95% CI 0.1–0.24) for class 2 vs. class 1; HR 0.34 (95% CI 0.28–0.41) for class 3 vs. class 1; HR 0.38 (95% CI 0.32–0.45) for class 4 vs. class 1 ($P < 0.001$); Figure 3].

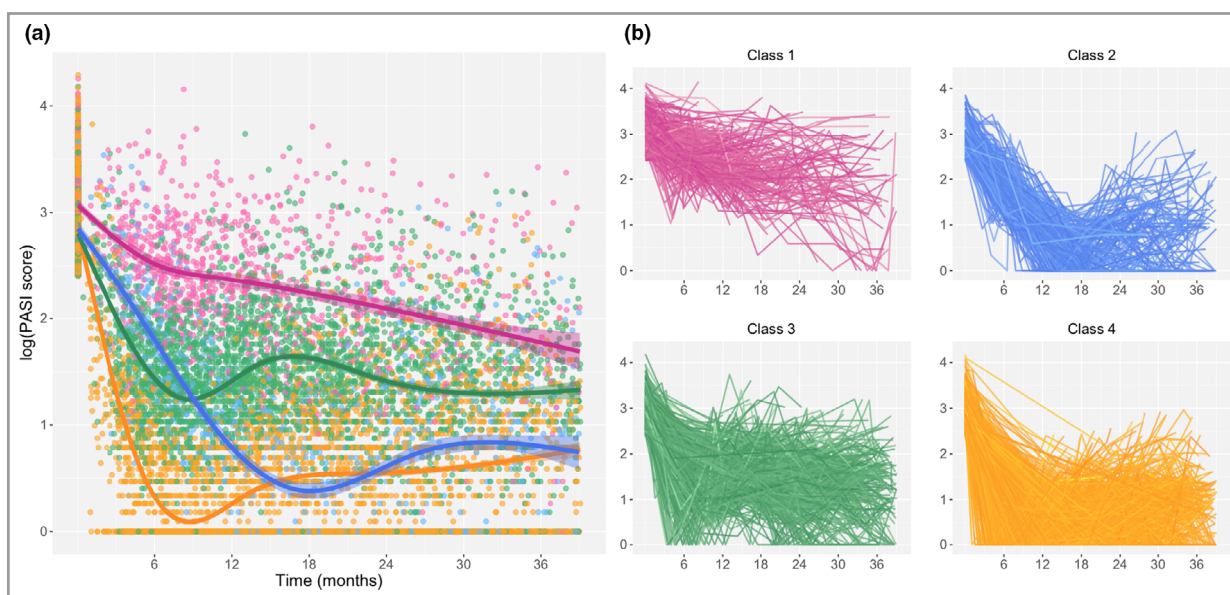


Figure 2 Resulting classes from a four-class latent class mixed model (pink = class 1; blue = class 2; green = class 3; orange = class 4). (a) Observed trajectories of log(PASI) over 3 years of follow-up. Plot lines represent a smoothing of the data (using a generalized additive model); shaded areas represent the 0.95 confidence interval. (b) Patient trajectories in each of the resulting classes (each line represents a single patient). PASI, Psoriasis Area and Severity Index.

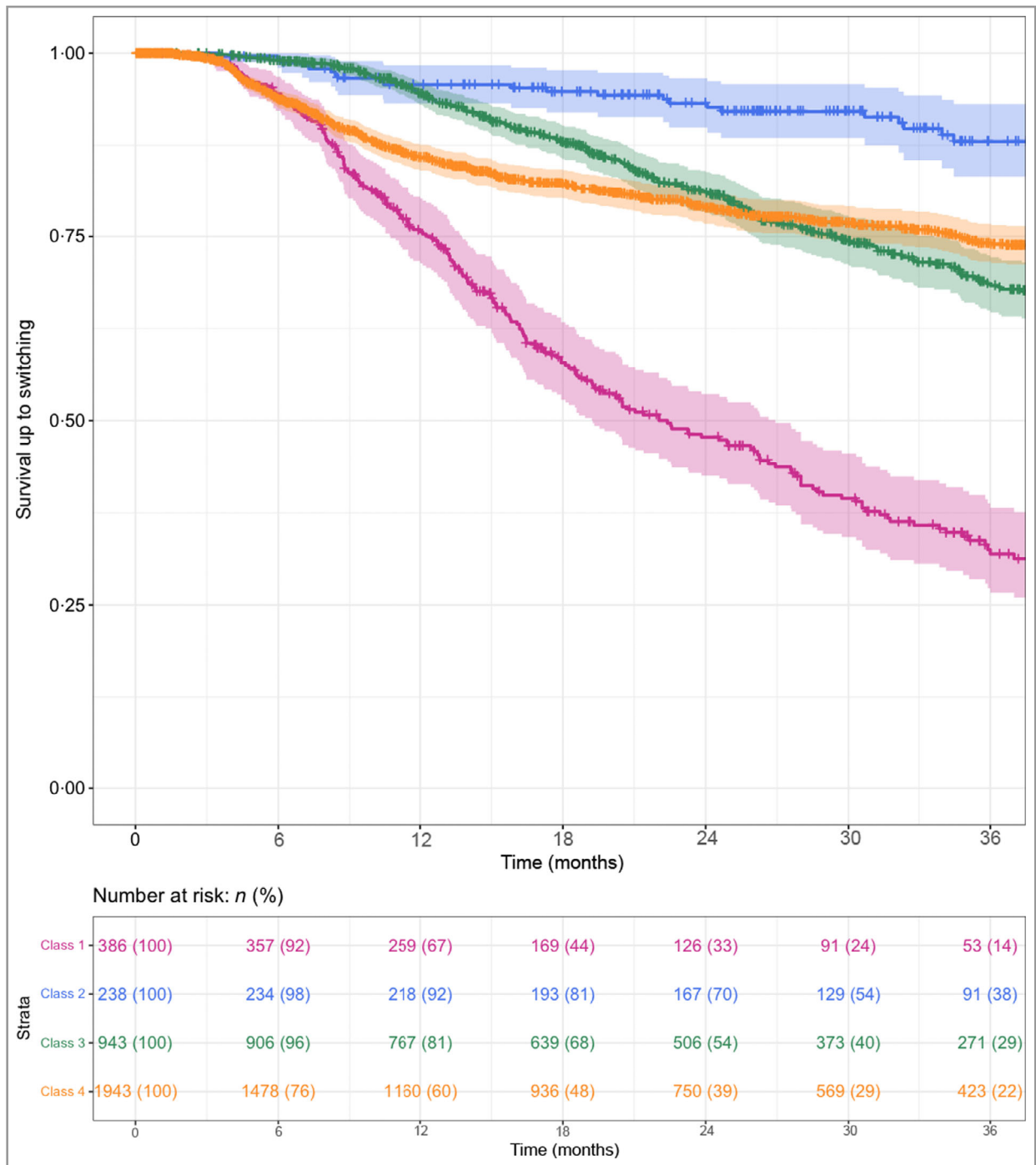


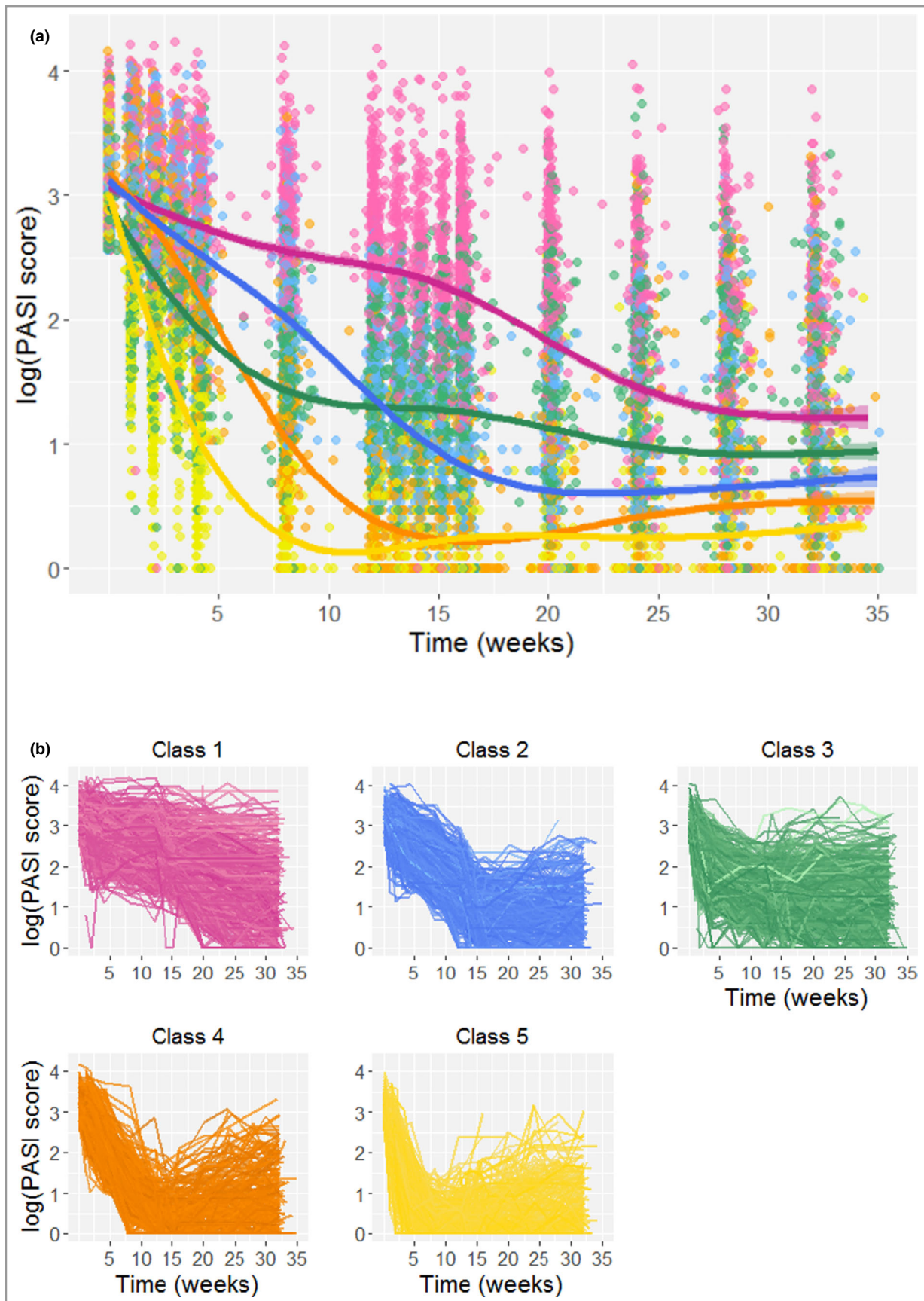
Figure 3 Analysis of time to switching from first-line biologic therapy in the four latent classes. Shaded areas represent the 95% confidence interval.

Five trajectories are identified in clinical trials

To assess the validity of the trajectory subgroups identified in the BADBIR data, we applied the LCMM to data pooled across

four clinical trials of biologics in psoriasis, containing 36 129 PASI measurements for 2889 participants over a 35-week observation period. This analysis identified five trajectories of response (Figure 4). Similar to the trajectory classes identified

Figure 4 Resulting classes from a five-class latent class mixed model (pink = class 1; blue = class 2; green = class 3; orange = class 4; yellow = class 5). (a) Observed trajectories of log(PASI) over 35 weeks of follow-up. Plot lines represent a smoothing of the data (using a generalized additive model); shaded areas represent the 95% confidence interval. (b) Patient trajectories in each of the resulting classes (each line represents a single patient). PASI, Psoriasis Area and Severity Index.



in the BADBIR dataset, class 1 (19.3% of the cohort), and class 3 (25.4%) demonstrated a moderate but sustained reduction in disease severity, with class 1 showing a slower rate of reduction in PASI. Class 2 (15.6%), class 4 (16.5%) and class 5 (23.1%) all demonstrated good initial reduction in disease severity (at varying rates) with a subsequent increase in PASI starting from about 20 weeks onwards. Class 5 demonstrated the highest mean (SD) BMI [31.1 (7.5); $P < 0.001$ (Table 2)] and had the highest proportion of patients treated with ixekizumab (a total of 66.2% of patients in class 5; $P < 0.001$). Over half of the patients in class 1 were treated with etanercept (52.1%; $P < 0.001$); patients in class 1 also tended to be younger [mean (SD) age 43.3 (13.8) years; $P = 0.008$].

The reproducibility and consistency of the four trajectory classes identified in BADBIR was further assessed by assigning participants from the clinical trials dataset to these trajectories by using PASI ranges at 3 and 6 months. Overall, using this approach, patterns from trial participants mimic those observed in the matching registry-identified classes, with class 2 showing a slightly more moderate reduction in disease severity (Appendix S2).

Genetic human leucocyte antigen biomarker associates with trajectories of response

We next investigated whether the HLA-C*06:02 allele, which confers the strongest genetic effect on psoriasis susceptibility and has been shown to be associated with biologic response,^{14,16} was associated with latent trajectory classes. Based on 1209 patients included in the LCMM analysis on the BADBIR cohort, HLA-C*06:02 was nominally associated with membership of two LCMM classes (see Table S1 in Appendix S2). Patients with more copies of the allele were more likely to be in class 3: 36.0% of patients with two

copies of HLA-C*06:02 were in this class vs. 31.1% of patients with one copy and 26.4% of HLA-C*06:02-negative patients ($P = 0.037$, unadjusted). Conversely, HLA-C*06:02 conferred decreased likelihood of being in class 1: 13.3%, 9.4% and 8.0% of patients with zero, one and two copies, respectively, were in this class ($P = 0.028$, unadjusted). These results suggest that HLA-C*06:02 status may influence patients' trajectories. Their potential relationship with other patient-specific features relevant to disease progression and response could be elucidated through the study of larger genotyped cohorts.

Discussion

Previous studies of stratification in psoriasis have focused on disease subtypes by clinical phenotype and application of machine learning to transcriptomic responses.^{17–19} Here we identified four distinct, universal, trajectory subgroups, based on longitudinal analysis of data collected within BADBIR. Notably, these subgroups demonstrated different mean patterns of change in disease severity over time and primarily differed with respect to time to, degree of and subsequent increase in disease severity. Further, these subgroups were characterized by various baseline clinical and genetic features.

Patients in classes 2 and 4 both demonstrated an initial reduction in disease severity followed by an overall increase, as defined by PASI, while those in class 3 demonstrated an initial steep reduction in disease severity followed by an overall maintenance. Interestingly, although classes 2 and 4 both achieved similar reductions in PASI at 18 months (Figure 2), the pattern of reduction in disease severity differed. This suggests that there may be differences in the underlying mechanisms by which the disease progresses in these patients and/or how they respond to therapy – a pattern that would not have been captured by conventional assessments of PASI 75

Table 2 Baseline characteristics of patients in the entire clinical trial cohort and in each of the five identified latent classes

	Entire cohort	Class 1	Class 2	Class 3	Class 4	Class 5	P-value
Patients (n)	2889	559 (19.4)	451 (15.6)	735 (25.4)	478 (16.5)	666 (23.0)	
Mean (SD) age at baseline (years)	44.9 (13.2)	43.3 (13.8)	45.9 (13.1)	44.7 (13.0)	45.3 (12.8)	45.7 (13.1)	0.008
Mean (SD) baseline PASI	20.4 (7.0)	18.1 (6.7)	18.0 (7.1)	23.1 (9.4)	22.2 (8.8)	22.6 (10.0)	< 0.001
Sex							< 0.001
Female	897 (31.0)	160 (28.6)	113 (25.1)	233 (31.7)	137 (28.7)	254 (38.1)	
Male	1992 (68.9)	399 (71.4)	338 (74.9)	502 (68.3)	341 (71.3)	412 (61.9)	
Mean (SD) BMI (kg m ⁻²)	29.8 (7.0)	28.2 (6.3)	30.7 (7.4)	28.8 (5.9)	30.0 (7.3)	31.1 (7.5)	< 0.001
Ethnicity							0.009
Asian	367 (12.7)	93 (16.6)	67 (14.9)	74 (10.1)	58 (12.1)	75 (11.3)	
Black	53 (1.8)	9 (1.6)	11 (2.4)	12 (1.6)	10 (2.1)	11 (1.6)	
White	2318 (80.2)	437 (78.2)	350 (77.6)	616 (83.8)	368 (77.0)	547 (82.1)	
Other	151 (5.2)	20 (3.6)	23 (5.1)	33 (4.5)	42 (8.8)	33 (4.9)	
Drug							< 0.001
Ixekizumab – 2 weeks ^a	639 (22.1)	59 (10.5)	83 (18.4)	170 (23.1)	107 (22.4)	220 (33.0)	
Ixekizumab – 4 weeks ^a	640 (22.1)	84 (15.0)	82 (18.2)	179 (24.3)	74 (15.5)	221 (33.2)	
Etanercept	652 (22.6)	291 (52.1)	110 (24.4)	164 (22.3)	54 (11.3)	33 (4.9)	
Secukinumab 150 mg	489 (16.9)	75 (13.4)	87 (19.3)	133 (18.1)	119 (24.9)	75 (11.3)	
Secukinumab 300 mg	469 (16.2)	50 (8.9)	89 (19.7)	89 (12.1)	124 (25.9)	117 (17.6)	

BMI, body mass index; PASI, Psoriasis Area and Severity Index. ^aInitial ixekizumab protocols, where for some patients the frequency of treatment changed after the first 12 weeks.

and PASI 90 response at a fixed timepoint. Further, therapy-specific patterns of change in PASI over time seem to be similar for the four biologics analysed in the BABIR data (Figure S3; see Supporting Information). Nevertheless, for these findings to be translated into a clinical tool, it may be beneficial to combine some of these classes. For example, classes 3 and 4, both of which show good response, may be merged to represent all good responders.

A high BMI in patients with psoriasis has previously been reported to have a significant effect on their prognosis and response to biologics, thereby reducing the rates of those achieving PASI 75.⁴ Here class 1 further captured this association of higher BMI and a reduced magnitude of change in PASI when treated with biologics.

While HLA-C*06:02 status has been previously associated with change in PASI response to biologics, particularly ustekinumab and adalimumab,¹⁴ we found only modest evidence for an effect on longitudinal patterns of PASI in patients treated with biologics, albeit supportive of future investigation.

To assess these trajectories, in a second cohort of patients, we applied our LCMM model to a dataset obtained from pharmaceutical company clinical trials of biologic therapies for psoriasis. This analysis objectively identified five trajectory cases as the best fit; these had overall good similarity to those identified in the registry dataset, with one low reduction, one moderate reduction and two good PASI reduction groups identified. There are several potential reasons why identical results were not obtained. Firstly, the registry dataset contains real-world data, where patients are likely to represent a more heterogeneous and complex population such as elderly patients, and those on polypharmacy and with multimorbidity. Patients in clinical trials are enrolled through strict criteria. Secondly, patients in the registry dataset, unlike in clinical trials, will likely be treated with various adjuvant treatments, such as methotrexate, to improve outcomes. Thirdly, the specific biologics used differ between the two populations, with only entanercept common to both. Finally, the duration of available follow-up differed between the two datasets. Nevertheless, the results obtained by our analysis of trial patients strengthen the observations made in the registry data: (i) the overlap between the five trajectories identified independently in the trials dataset and the four identified in the registry data [Figures 3 and 4, and Figure S4 (see Supporting Information)]; and (ii) the similarity in the overall shapes of assigned (by PASI range criteria at two timepoints) trajectories in trials data and the initial, early-in-treatment, trajectories in the BADBIR data (Appendix S2).

For the analyses presented here, patients treated with any of the biologic therapies (in the BADBIR cohort or the clinical trials data) were pooled together; this was done to generate sufficiently large datasets for identification of universal trajectories of disease following initiation of biologic therapy. An analysis of the adalimumab-treated subgroup alone – the largest available in BADBIR – resulted in the fit of a four-class model, demonstrating robust results to those obtained by analysing the pooled BADBIR dataset (Figure S2). However,

whereas therapy-specific patterns of change in PASI over time seem similar for the four analysed biologics (Figure S3), as this and other registries accumulate more data, future studies will be able to discriminate between individual biologic trajectories.

We did not identify a no-change, worsening or lack-of-response subgroup, even though such patients are encountered in clinical practice. One possible explanation is incomplete representation of patients whose disease worsens over time, as these may be switched to a second biologic and our analysis was restricted to first-line therapy. Further, informative missingness may have also affected the shape of the trajectories of each class. We partially mitigated this through the analysis of differences in the time to switching from first-line therapy between the four resulting classes; this demonstrated that patients in class 2 had a lower rate of switching, while class 1 showed higher rates (Figure 3). It is plausible that class 1 is affected by this risk of bias, and that the PASI measures in this group were, in reality, higher than seen in Figure 2. It is conceivable that a fifth subgroup may exist in which patients show no improvement with biologic therapy and were not captured by our approach. Future studies should incorporate therapy switches as an indicator of response within the subgroup discovery algorithm to allow further validation.

Differences were found between the classes in duration of follow-up. Individuals in class 2 had the longest mean (SD) duration of follow-up [2.0 (0.8) years] and those in class 4 the shortest [0.9 (1.1) years]. It is conceivable that these differences were partially driven by variation in response to therapy, thus inducing informative dropout from our study for which we could not adjust our analyses.

Interestingly, a no-change or non/low-response subgroup was also missing from the clinical trials dataset. One possible explanation is selection bias, which has been shown to be a common phenomenon in clinical trials.²⁰ This may, at least in part, present itself in the exclusion of patients with hypertension and diabetes (known to have worse disease and poorer responses to biologic therapy) from at least two of the trials included in the pooled dataset. Alternatively, the absence of a nonresponder group, from both analyses, could be the result of the rarity of such patients who lack a primary response.

A potential introduction of bias caused by the exclusion of patients with incomplete baseline information (24.7% of available patients on first-line biologic therapy with a baseline PASI ≥ 10 within the registry dataset) may have been possible; the LCMM implementation requires complete information for any covariates included in the model. While multiple imputation could eliminate this potential bias, given the large number of patients in our dataset and that missing covariate data were likely missing completely at random, a complete case approach remains robust.

A key strength of this study is the longitudinal nature and quality of the BADBIR dataset, including detailed disease severity assessments and phenotypic characterizations. These rich data enabled not only the identification of latent classes, but also meaningful clinical characterization of these. Our findings from

clinical trials data further strengthen these findings, and assessment of potential genetic biomarkers suggests that the classes may represent different biological mechanisms. This study is a landmark in psoriasis research as it demonstrates the value of data-driven approaches to using high-quality registries and clinical trial data to generate hypotheses for precision medicine. However, it should be noted that the subgroups discovered by our analysis do not necessarily represent distinct subtypes of psoriasis, but represent courses of disease progression following the initiation of biologic therapy. Our approach is hypothesis generating and requires further validation and investigation of the underlying mechanisms. As some of the clinical and outcome characteristics overlap between the identified trajectory groups, it would be difficult to use these for individual patient prediction. Nevertheless, this is the start of the process of grouping patients based on longitudinal patterns of response. Our next steps will involve identifying panels of genetic and molecular biomarkers that can better predict class memberships and response to therapy, and add these to the model.

To the best of our knowledge, this is the first study to take a data-driven, longitudinal, statistical modelling approach for patient stratification in psoriasis by identifying subgroups of longitudinal patterns of disease progression. This study has uncovered some plausible subgroups of patients with psoriasis, based on disease course over time, which may prove, with further causal investigation, to be distinct endotypes. These could potentially be useful in the stratification and prediction of response to biologic therapy, thereby improving clinical trial design and enabling targeted research and future developments of therapies. Investigation of drug-specific trajectories, as well as combining these LCMM classes with molecular data, will provide putative endotypes with greater discovery potential than current clinical labels when exploring associations in respect of biological mechanisms.

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Appendix

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Members of the Data Monitoring Committee and the BADBIR Steering Committee.

Appendix S2 Latent class analysis and trajectory assessment in clinical trial data.

Figure S1 Model selection based on fit and percentage of patients as a function of the number of classes.

Figure S2 Resulting classes from a four-class latent class mixed modelling in adalimumab-treated patients.

Figure S3 Therapy-specific patterns of change in Psoriasis Area and Severity Index over time.

Figure S4 Comparison between trajectories identified in the British Association of Dermatologists' Biologics and Immunomodulators Register dataset and those identified in the clinical trials data.