Identification of factors that may influence the selection of first-line biologic therapy for people with psoriasis

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Identification of factors that may influence the selection of first-line biologic therapy for people with psoriasis: a prospective, multi-centre cohort study

Running head

What drives the choice of first-line biologic for psoriasis?

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Bulleted statements (max 70 words per question)

What's already known about this topic?

- Previous research has explored the effectiveness and safety of different biologic therapies for people with psoriasis.
- The factors which predict whether or not a person with psoriasis will start a biologic therapy have been identified.

What does this study add?

- Identifies factors that influenced how dermatologists chose between adalimumab, etanercept, and ustekinumab for people with psoriasis. Statistically significant factors included: presence of psoriatic arthritis, patient weight, registration country, employment status, and disease severity.
- Suggests that dermatologists change their prescribing behaviour in line with experiences and emerging evidence on treatment effectiveness and safety.

Provides baseline data to inform the evaluation of new strategies which may influence prescribing.

Summary

Background

The Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium has a collective aim to develop a prescribing algorithm to help stratify eligible psoriasis patients to the most appropriate biologic treatment. To facilitate the adoption of a stratified approach, it is necessary to first understand the factors driving the choice of first-line biologic therapy.

Objectives

To identify and quantify factors which influence the selection of the first-line biologic therapy for people with psoriasis.

Methods

Multinomial logistic regression was used to determine the factors which influenced the probability of treatment selection, using data from the British Association of Dermatologists Biologic Interventions Register (BADBIR) from January 2012 to December 2015. Sensitivity analyses were performed to assess the robustness of the findings to key assumptions.

Results

The main analysis was based on a dataset comprising 3,040 people with psoriasis. The identified factors affecting first-line biologic selection within the available therapies were: presence of psoriatic arthritis; patient weight; employment status; country of registration; and baseline disease severity. Importantly, the analysis showed a general shift in prescribing behaviour over time. These results were robust to sensitivity analysis.

Conclusions

This study offers important insights into the factors influencing current prescribing practice for first-line biologic therapies for people with psoriasis. It provides baseline data to inform the evaluation of future potential changes that may impact prescribing behaviour such as stratified medicine.

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disorder, affecting around 2% of the population in the United Kingdom (UK).[1] A range of biologic therapies are available to treat psoriasis which target different mediators of the disease. In 2017, the current clinical guidelines for psoriasis made recommendations for six biologic therapies.[2–4] These consist of: three tumour necrosis factor alpha (TNF-α) inhibitors (adalimumab, etanercept and infliximab); one interleukin-12/interleukin-23 (IL-12/23) inhibitor (ustekinumab); and two IL-17 inhibitors (secukinumab and ixekizumab).

Biologic therapies are recommended by the National Institute for Health and Care Excellence (NICE) for people with psoriasis who have tried, failed, or are unsuitable for, methotrexate/ciclosporin, acitretin and phototherapy. Specific criteria based on disease severity and health-related quality of life are used to inform eligibility to start a biologic therapy.[2] To be eligible for a biologic therapy which is not infliximab, the person with psoriasis must have a total Psoriasis Area and Severity Index (PASI) ≥ 10 and a Dermatology Life Quality Index (DLQI) > 10. For infliximab, the thresholds for prescribing are higher (PASI ≥ 20 and DLQI > 18).

The Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium has a collective aim to develop a clinical prescribing algorithm to help stratify people with psoriasis to the most appropriate first-line biologic therapy.[5] The rationale for predicting the optimal *first-line* biologic is to overcome the limitations of "trial and error" prescribing, which is costly both to the health service and to the patient. To facilitate the adoption of stratified medicine for psoriasis, and to accurately describe the potential added value of implementing a stratified approach, it is necessary to understand how first-line biologics are currently prescribed.

NICE guidelines state that when offering systemic therapy, clinicians should tailor the choice of agent and dosing schedule to the needs of the patient.[2] These guidelines also state that treatment selection should include consideration of: the person's age; disease phenotype; pattern of activity; previous treatment history; disease severity and impact; the presence of psoriatic arthritis (PsA); conception plans; comorbidities; and the views of the person with psoriasis.[2] However, NICE does not provide an explicit indication about how prescribing clinicians should use these suggested factors to choose between treatments. The British Association of Dermatologists (BAD) have also published guidelines which made recommendations for adalimumab, etanercept, infliximab, and ustekinumab in October 2009.[6] In these guidelines, TNF-α inhibitors were favoured as the first-line biologics of choice over ustekinumab due to a limited evidence base for its safety and effectiveness at the time of publication. The BAD guidelines are currently being updated.[7]

The cost to the NHS in the UK and to the Health Service Executive in the Republic of Ireland (ROI) of each biologic therapy is similar,[3] while there is evidence to suggest that there is some heterogeneity

in the probability of response for each biologic therapy. Head-to-head studies have demonstrated the superiority of ustekinumab,[8] secukinumab,[9] infliximab,[10] and ixekizumab[11] over etanercept in terms of achieving 75% and 90% reductions in PASI (PASI 75 and PASI 90). Furthermore, a recent head-to-head study has shown the superiority of secukinumab over ustekinumab in terms of PASI 90.[12]

The aim of this study was to identify and quantify factors which influence the choice of first-line biologic therapy for people with psoriasis. The study objectives were: to quantify the relative impact of factors suggested in NICE guidelines to influence the selection of a biologic therapy; to test additional factors other than those specified in NICE guidelines; and to illustrate how prescribing patterns for biologic therapies have changed over time.

Patients and methods

Regression-based methods were used in this analysis. All statistical analyses were performed using STATA version 13 (STATA Corp., Texas, USA). In accordance with standard practice, the statistical significance level was set at 5% (P < 0.05). Data were taken from the British Association of Dermatologists Biologic Interventions Register (BADBIR) – a long-term pharmacovigilance register of people with moderate-to-severe psoriasis for whom safety and clinical information is collected along with response to different biologic and conventional therapies.[13] People with psoriasis have been prospectively recruited by participating clinicians in 153 dermatology centres in the UK and ROI since 2007. Figure 1 shows the numbers of people with psoriasis in BADBIR treated using biologics and conventional therapies, and provides a descriptive summary of the first biologic therapy prescribed for those who were biologic-naïve. As of 1st January 2016, there were data for 11,303 patients. Of the 7,316 patients in BADBIR with exposure to biologic therapy, data were collected and recorded for 5,882 patients who were biologic-naïve.

<Figure 1 Here>

Statistical analysis

Multinomial logistic regression was used to estimate which factors influenced the probability of selecting each biologic therapy. The dependent variable was categorical to identify the initial biologic received by each patient. The analysis focused on the biologic therapies which were most prescribed during the study period (adalimumab, etanercept and ustekinumab). Independent variables were the potential influences on treatment selection. Independent variables were identified from NICE guidelines (patient age, disease phenotype, previous treatment history, disease severity, presence of PsA, presence of any comorbidity) and to test further hypotheses (patient weight, gender, ethnicity, smoking status, alcohol status, employment status, whether the registration country was UK or ROI, and a time trend variable). Definitions of the variables used in the analysis are presented in Table 1.

<Table 1 Here>

The analysis used centre-level fixed effects to account for unobserved factors, such as patient mix and local care pathway guidelines, which varied between centres and may have influenced the probability of biologic therapy selection. This was achieved by including the centre variable in the

regression, and centres with smaller numbers of patients (n<10) were grouped into a single centre to allow for regressions to converge and control for centre size.

To interpret the output of the regression, average marginal effects were calculated. Marginal effects indicate how changes in the independent variables are associated with changes in the probability of choosing each biologic therapy, while controlling for all other variables.

The following data within BADBIR were excluded from this analysis: (1) people who started a biologic therapy before 2012 (a 2012 cut-off allowed us to explore changes in prescribing over time, while using sufficiently recent data to ensure that results were reflective of 'current practice' and newly published clinical guidelines for psoriasis[2]); (2) people whose first biologic therapy was efalizumab, infliximab or unknown (to focus on the main first-line biologics prescribed in current practice); (3) people without an observation that occurred within 6 months before starting biologic therapy (to allow us to interpret patient characteristics at 'baseline'); and (4) people with missing data in the variables of interest in their 'baseline' observation.

In BADBIR, data were not always collected on the treatment start date and in these instances it was difficult to define 'baseline' characteristics. The closest observation before the start date of a biologic therapy, within six months, was taken as the baseline measurement.[14] Two sensitivity analyses were performed. One sensitivity analysis used only people with psoriasis who had a PASI ≥ 10 such that inclusion criteria adhered to NICE guidelines. A second sensitivity analysis used an alternative definition for baseline. Baseline was re-defined as the observation closest to the start date for the biologic therapy (before or after). These two sensitivity analyses attempted to explore the robustness of the findings in the primary analysis.

Results

Figure 2 shows a timeline of NICE technology appraisals (TAs) and clinical guidelines which recommended biologics for psoriasis (above the timeline) and PsA (below the timeline). Figure 3 shows the number of biologic-naïve psoriasis patients starting treatment for each biologic in each year within the dataset. It is evident that there was a significant shift in the use of each biologic over time. Adalimumab became the standard choice of first-line biologic therapy from 2010 onwards (65% of initial biologic prescriptions in 2015), and the use of ustekinumab has risen since its approval in 2009 (now 27% of initial biologic prescriptions). In contrast, the proportion of first-line biologic prescriptions of etanercept had fallen to around 8% and infliximab to 0% in this dataset (prescriptions for infliximab were not registered to BADBIR over the past two years as Merck Sharp & Dohme decided not to continue). The marketing licence for efalizumab was withdrawn in 2009. There were no data on secukinumab as it was only licensed for use in psoriasis in 2015 and the data cut-off is too early to capture it. The sample size in 2015 was lower than previous years. This is because the uptake of biologic therapies has led to a reduction in the number of people with psoriasis who could start their first biologic, and more patients are progressing to second-line biologic therapy.

<Figure 2 Here>

<Figure 3 Here>

<Figure 4 here>

Figure 4 shows how the final dataset comprising 3,040 people with psoriasis was obtained and Table 2 reports the summary statistics for the final sample of patients. The average age of the sample was 44.6 years old and 40% were female. Within the sample, 28% of people weighed over 100kg. Further analysis found that 80% of people were classified as overweight or obese (Body Mass Index ≥ 25), compared with 58% in the general population.[15]

Three quarters of the sample were either employed or a full-time student. For those of working age in the UK (n=2,835), the unemployment rate in the sample was 20.8%. This was much higher than the UK average unemployment rate which peaked at 8.2% between 2012 and 2015.[16] The unemployment rate for those of working age in the ROI (n=143) was 17.5%, which was closer to the ROI average unemployment rate which peaked at 15% between 2012 and 2015.[17]

People with psoriasis within the sample received an average of two systemic therapies before starting a biologic therapy. Further investigation of previous treatments found that 63% of the sample had exposure to methotrexate, 49% had taken ciclosporin, 39% had taken acitretin, and 13% had taken fumaric acid esters. Exposure to ultra-violet (UV) radiation therapies such as UVA (long-wave UV), PUVA (psoralen combined with UVA) and UVB (short-wave UV) was recorded as 26% and 62% for PUVA/UVA and UVB respectively. The observed prior therapies in the sample are in keeping with the expected sequence of treatments that lead a person with psoriasis to be prescribed a biologic therapy.[18]

The mean PASI of the sample was 15.9 (median 14.2) which indicates a population with severe psoriasis (PASI records ranged from 0 to 67.8). Compared with the general population in which 19% of people smoke,[19] a larger proportion (31%) of the sample reported that they smoked at the time of their baseline consultation; 67% had reported ever smoking. Furthermore, nearly three quarters of the sample (71%) reported drinking alcohol, compared with 58% in the general population.[20] The majority (98%) of the sample had chronic plaque psoriasis; 22% of the sample had PsA and 69% had at least one comorbidity as defined by the BADBIR registry.

<Table 2 Here>

Primary analysis

Table 3 reports the estimated marginal effect of each variable on selecting one of the three specified biologic therapies. There was an increased probability of prescribing ustekinumab for a person weighing over 100kg by 0.07 (7 percentage points) and reduced probabilities of prescribing adalimumab or etanercept. The presence of PsA increased the chances of adalimumab being selected by 10%, and reduced the chances of ustekinumab selection by 8%. Notable statistically significant effects on treatment selection were observed for a patient's employment status. Relative to someone in employment, people who were unemployed or on sick leave were more likely to receive ustekinumab and less likely to receive adalimumab. The same was true for those in retirement. Disease severity (as measured by PASI) had a small but statistically significant effect on the probability of treatment selection. A unit increase in the baseline PASI (increase in severity) was associated with a 0.3% lower chance of choosing etanercept and 0.2% increased chance of choosing ustekinumab. Therefore, a five unit increase in the baseline PASI would be associated with a 1.5%

lower chance of choosing etanercept, and a 1% increased chance of choosing ustekinumab. Gender was also found to affect the selection of biologic (females more likely to receive adalimumab and less likely to receive ustekinumab). Patients who were registered in the ROI were 13% more likely to receive etanercept than their UK counterparts over the study period.

The analysis showed a statistically significant effect of 'year' on the selection of all three of the included biologic therapies. For each additional year between 2012 and 2015, people with psoriasis were on average: 5% less likely to be treated with etanercept; 3% more likely to be treated with adalimumab; and 2% more likely to be treated with ustekinumab.

<Table 3 Here>

No patterns emerged for treatment selection based on the presence of different types of psoriasis. Furthermore no statistically significant effects were found on treatment selection of age, ethnicity, patient behaviour (smoking and alcohol), disease duration, previous treatments, and whether or not the person had any comorbidities. The prescribing centre variable was used to control for centre-level characteristics such as patient mix and local care pathway guidelines. The results for this variable cannot be reported (to protect anonymity) but there were centres with statistically significant effects and the inclusion of the variable reduced omitted variable bias.

Sensitivity analyses

Two sensitivity analyses were performed to explore the robustness of the results (see supplementary appendix for the tabulated results). Including only people with a PASI ≥ 10 (to adhere with NICE guidelines), reduced the eligible sample size from 3,040 to 2,676 people with psoriasis. Using an alternative definition for baseline increased the eligible sample size (n=3,459). Overall the results remained stable and the statistically significant results in the main results were robust. The exception to this was gender for which the result was no longer statistically significant with an alternative baseline definition.

Discussion

This study provides robust, real-world evidence from a substantial sample of people with psoriasis that the choice of first-line biologic was influenced by a number of factors: the year of treatment commencement; country of registration (UK or ROI); presence of PsA; patient weight; employment status; and disease severity. The most statistically significant driver of treatment selection was the time trend variable (year of treatment commencement). While the time trend variable reflects changes in recruitment to BADBIR, it is likely that this is reflective of overall prescribing behaviour due to the large number of participating centres. Changes over time could be indicative of the emergence of evidence on effectiveness, the increasing experience of prescribing clinicians, and the adoption of more effective treatments. The primary analysis considered people with psoriasis registered on BADBIR between 2012 and 2015. It is important to note that the most frequently registered first-line biologic for psoriasis up to 2009 was etanercept but this changed to adalimumab from 2010 onwards. In the UK, the shift towards adalimumab and, more recently, ustekinumab may be a reflection of emerging evidence to suggest that etanercept is less effective.[8,9,11] In contrast, the findings showed that etanercept use remained relatively high in the ROI, potentially due to its long term safety record. The Health Service Executive (the Irish equivalent of the NHS) are not affiliated

with NICE and it is also possible that dermatologists in the Republic of Ireland still follow BAD biologics guidelines from 2009,[6] in which adalimumab and etanercept were recommended as first-choice over ustekinumab.

The presence of PsA influenced the selection of a biologic therapy, which was likely to be because anti-TNF biologics (adalimumab, etanercept, and infliximab) have demonstrated a higher probability of improvement for people with PsA when compared with ustekinumab using American College of Rheumatology outcomes (ACR20).[21–24] This differential response-rate meant that the anti-TNF biologics were recommended for the treatment of PsA before 2012.[25] In contrast, ustekinumab was only recently recommended by NICE for PsA in June 2015, and only for patients who have not responded to or are unsuitable for anti-TNF treatment.[26]

A high prevalence of obesity in psoriasis patients is well established,[27] and this analysis identified a quantifiable effect for patient weight. Adalimumab and etanercept are mainly prescribed using a fixed dose and, as a result, it may be that people of higher weight have a poorer response to these biologics. Therefore, it is possible that clinicians selected the biologic therapy (ustekinumab) that allowed them prescribe a higher dose for people with a higher weight. Further work is needed to determine whether this was driven by considerations of cost-effectiveness, as the Patient Access Scheme for ustekinumab dictates that the 90mg dose (for patients over 100kg) should cost the same as the standard 45mg dose.[28]

People with psoriasis who were on sick leave, unemployed, or retired were more likely to receive ustekinumab. This finding suggests that clinicians deliberately chose ustekinumab for these groups, potentially because adherence may be a concern, because it is typically administered every 12 weeks (less frequently than anti-TNFs) and by a healthcare practitioner rather than self-administered. Furthermore, people with higher baseline disease severity (as measured by PASI) were more likely to receive ustekinumab, and less likely to receive etanercept. The decision to prescribe ustekinumab over etanercept for people with greater disease severity may be driven by the implied need for a more effective treatment.[29]

This study has, therefore, identified clear potential reasons that explain why the year of treatment commencement, country of registration (UK or ROI), presence of PsA, high patient weight, employment status, and disease severity may have had an impact on the choice of biologic. Moreover, characteristics which had no impact on biologic choice (e.g. type of psoriasis outside of PsA) were considered to be in keeping with expectations. Considerations of drug safety, drug persistence, and drug cost are also expected to influence drug choice. Factors such as these cannot be included in this type of regression analysis as they are characteristics of the drugs themselves, and would 'perfectly predict' the outcome (the choice of biologic). However, drug characteristics have helped us to explain the main findings in our study. After accounting for relevant covariates, recent evidence suggests that biologic-naïve patients with psoriasis are more likely to persist with ustekinumab treatment when compared with adalimumab and etanercept.[30] An awareness of these data may also have an influence on treatment selection in the future.

Previous research into the preferences of people with psoriasis has suggested that the groups with stronger preferences for less frequent treatments (e.g. ustekinumab) were women and the working population,[31] while our analysis found that these preferences were not met. A recent comparison of dermatologist and psoriasis patient preferences has highlighted the potential for improved patient

care following better communication between these groups.[32] There may be an important role to play for shared decision making and the use of patient decision aids in the context of dermatology.[33]

The importance of understanding the drivers of treatment choice is emphasised by the increasing complexity for clinicians and patients in selecting a first-line biologic, with a larger number of candidate drugs becoming available. Two IL-17 inhibitors (secukinumab and ixekizumab) have recently been recommended by NICE for treating moderate to severe plaque psoriasis.[3,4] Recommendations were made subject to the same conditions as those for adalimumab, etanercept, and ustekinumab. The IL-17 inhibitors may become first-line biologics of choice due to their high efficacy in terms of PASI 90.[9,11]

The analysis was limited in that it could not capture the effect of DLQI, a reflection of the health-related quality of life of the person with psoriasis, on the choice of biologic due to substantial missing data for this variable in the closest observation to the start of treatment. Previous adverse events experienced by patients, as well as patient and physician preferences were also expected to influence treatment selection and could not be directly included in this analysis. Another limitation was that testing for multiple potential factors may have increased the likelihood of a type-II error in the statistical analysis. However, this was unlikely as two sensitivity analyses confirmed the robustness of the primary analysis even when different assumptions were made.

Conclusions

This study provides important insights into the factors influencing the current prescribing practice of dermatologists in the UK and ROI selecting a particular first-line biologic therapy for people with psoriasis. The nature of BADBIR ensures that observational data reflecting actual clinical practice were used and, as such, the results are generalisable across the UK and the ROI. This study provides the baseline data to inform the evaluation of future potential changes that may influence prescribing behaviour, such as stratified approaches to the use of biologic therapies for people with psoriasis.

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Tables

Table 1: Definitions of variables used in the regression analysis

Variable	Description	Type
Outcome Variable		
First Biologic	The initial biologic received by the patient. =1 for adalimumab, =2 for etanercept, =3 for ustekinumab	Categorical
Patient Characteristics		
Age	Patient's age	Continuous
Female	=1 if female	Dummy
Weight Over 100kg	=1 if bodyweight is more than 100kg	Dummy
Ethnicity	=1 if white ethnicity	Dummy
Patient Behaviour		
Smokes	=1 if self-reported that they currently smoke	Dummy
Drinks Alcohol	=1 if self-reported that they currently drink alcohol	Dummy
Employment Status		
Work1	=1 if in full/part-time employment, a full time student or works full-time at home	Dummy
Work2	=1 if unemployed but seeking work, or not working due to disability/ill health	Dummy
Work3	=1 if retired	Dummy
Disease Characteristics		
PASI	Baseline PASI score	Continuous
DLQI	Baseline DLQI score	Continuous
Years With Psoriasis	Number of years the patient has had psoriasis	Continuous
Total Previous Systemics	Number of non-biologic systemic therapies the patient has had previously	Continuous
Chronic Plaque	=1 if the patient has chronic plaque psoriasis	Dummy
Seborrhoeic	=1 if the patient has seborrhoeic psoriasis	Dummy
Flexural	=1 if the patient has flexural psoriasis	Dummy
Scalp	=1 if the patient has scalp psoriasis	Dummy
Palms	=1 if the patient has psoriasis of the palms	Dummy
Nails	=1 if the patient has nail psoriasis	Dummy
Erythrodermic	=1 if the patient has erythrodermic psoriasis	Dummy
Guttate	=1 if the patient has guttate psoriasis	Dummy
Has PsA	=1 if the patient has psoriatic arthritis	Dummy
Has Comorbidity	=1 if the patient has one or more comorbidity	Dummy
Other		
Republic of Ireland	=1 if registration country is Republic of Ireland	Dummy
Year	The year the patient commenced biologic therapy	Continuous
Centre	The prescribing centre (used as a control)	Categorical

Table 2: Summary statistics for included independent variables (n=3,040 people with psoriasis)

Variable	Value
Patient characteristics	
Age (years), mean ± SD	44.64 ± 13.21
Female	40
Weight Over 100kg	28
Ethnicity	92
Patient behaviour	
Smokes	31
Drinks Alcohol	71
Employment status	
Work1 (Working or student)†	75
Work2 (Unemployed)	15
Work3 (Retired)	10
Disease characteristics	
PASI (Score), mean ± SD	15.88 ± 7.65
Years With Psoriasis, mean ± SD	21.14 ± 12.58
Total Previous Systemics, mean ± SD	2.03 ± 1.58
Chronic Plaque	98
Seborrhoeic	16
Flexural	37
Scalp	73
Palms	19
Nails	56
Erythrodermic	5
Guttate	13
Has PsA	22
Has Comorbidity	69
Other	
Republic of Ireland	5
Year, mean ± SD	2013.42 ± 1.07

Data are (%) unless otherwise stated.

† denotes a categorical variable omitted in regressions to prevent multi-collinearity.

Feasible range of PASI: 0-72.

Table 3: Estimated impact of unit changes in variables on the probabilities of selecting each biologic

| Variable [a] | Change in probability for unit changes in variable [b] | | |
	Adalimumab (n=1,993)	Etanercept (n=388)	Ustekinumab (n=659)
Age	-0.00	0.00	0.00
Female	**0.04***	-0.00	**-0.04***
Weight Over 100kg	**-0.04***	**-0.03***	**0.07***
Ethnicity	0.05	-0.01	-0.04
Smokes	0.01	-0.00	-0.01
Drinks Alcohol	0.03	-0.01	-0.02
Work2 (Unemployed)	**-0.05***	-0.00	**0.05****
Work3 (Retired)	-0.04	-0.00	**0.06***
PASI (Score)	0.00	**-0.00****	**0.00***
Years With Psoriasis	0.00	0.00	-0.00
Total Previous Systemics	0.01	-0.00	-0.01
Chronic Plaque	-0.02	0.06	-0.04
Seborrhoeic	0.01	0.02	-0.02
Flexural	0.00	-0.00	0.00
Scalp	-0.03	0.01	0.02
Palms	-0.00	0.01	-0.01
Nails	0.02	-0.02	0.00
Erythrodermic	-0.04	0.04	-0.00
Guttate	-0.00	0.01	-0.01
Has PsA	**0.10****	-0.02	**-0.08****
Has Comorbidity	0.00	0.01	-0.01
Republic of Ireland	-0.07	**0.13****	-0.06
Year	**0.03****	**-0.05****	**0.02****

*Statistically significant at p<0.05, ** statistically significant at p<0.01, *** statistically significant at p<0.001.*

[a]Work1 (Working or student) was omitted in regressions to prevent multi-collinearity.

[b]The changes in probabilities for unit changes in each variable are termed 'average marginal effects'.

Figure Legends

Figure 1: People with psoriasis enrolled in BADBIR on 1st January 2016

*The marketing licence for efalizumab was withdrawn in 2009.
No data on the use of secukinumab as a first-line biologic were available to include in this analysis as secukinumab patients were not actively recruited to BADBIR until January 2016.

Figure 2: Timeline of NICE recommendations for psoriasis and psoriatic arthritis treatments

TA = Technology Appraisal. CG = Clinical Guideline. Psoriasis guidance is above the timeline. Psoriatic arthritis guidance is below the timeline.

Figure 3: Number of biologic-naïve people with psoriasis starting a biologic therapy in a given year

The following biologics were omitted from this figure due to low sample sizes: infliximab (n=116 in total, n=1 in 2014, n=0 in 2015); efalizumab (n=11); "clinical trial biologic" (n=2); secukinumab (n=0).

Figure 4: Flow diagram of study eligibility

At a sample size of 3,387, numbers of missing data were: DLQI (1,926), Weight Over 100kg (103), Smokes (177), Work1-3 (68), Drinks Alcohol (45), Years With Psoriasis (31), Has PsA (9), Ethnicity (6). DLQI score omitted from analysis due to substantial missing data in the closest observation to the start of treatment.

istically significant effects that were robust to sensitivity analysis.

Biologic Cohort flow diagram:

- 1st January 2016 n=11,303
  - Biologic Cohort n=7,316 (65%)
    - Had Previous Biologic n=1,434 (20%)
    - First Biologic n=5,882 (80%)
      - Adalimumab n=3,375 (57%)
      - Etanercept n=1,398 (24%)
      - Infliximab n=116 (2%)
      - Ustekinumab n=980 (17%)
      - Efalizumab* n=11 (0%)
      - "Clinical trial biologic" n=2 (0%)
  - Conventional cohort n=3,987 (35%)

Timeline:

Above the line:
- Infliximab (TA134) 23/1/2008
- Adalimumab (TA146) 25/6/2008
- Etanercept and Efalizumab (TA103) 26/7/2006
- Ustekinumab (TA180) 23/9/2009
- Psoriasis Clinical Guidelines (CG153) 24/10/2012
- Secukinumab (TA350) 22/7/2015

Timeline bar: 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015

Below the line:
- 26/7/2006 Etanercept and Infliximab (TA104)
- 22/8/2007 Adalimumab (TA125)
- 25/8/2010 Adalimumab, Etanercept, Infliximab (TA199)
- 4/6/2015 Ustekinumab (TA340)

5,882	Number of people with psoriasis in BADBIR exposed to their first biologic
3,913	Number of people with psoriasis after exclusion of those who started biologic treatment before 2012
3,865	Number of people with psoriasis after exclusion of those whose first biologic was infliximab, efalizumab, or not known
3,387	Number of people with psoriasis after exclusion of those without a 'baseline' observation (within 6 months before the start date of biologic treatment)
3,040	Number of people with psoriasis after exclusion of those with missing data in any of the included factors