Cost-Effectiveness Analysis of Sequential Biologic Therapy with Ixekizumab Versus Secukinumab in the Treatment of Active Psoriatic Arthritis with Concomitant Moderate-to-Severe Psoriasis in the UK

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Abstract

Background Interleukin-17A (IL-17A) antagonists are a recent innovation for treating psoriatic arthritis (PsA). There are currently no cost-effectiveness analyses (CEAs) comparing the IL-17A antagonists ixekizumab and secukinumab in PsA from a UK perspective.

Objective We conducted a CEA from the UK National Health Service perspective to compare ixekizumab versus secukinumab in patients with PsA and concomitant moderate-to-severe plaque psoriasis.

Methods A Markov model was developed based on the widely accepted York model. In biologic disease-modifying anti-rheumatic drug (bDMARD)-naïve patients, ixekizumab → ustekinumab → best supportive care (BSC) was compared with secukinumab → ustekinumab → BSC. For bDMARD-experienced patients, ixekizumab → BSC was compared with secukinumab → BSC. At the end of the bDMARD trial period, Psoriatic Arthritis Response Criteria (PsARC) responders continued to receive the bDMARD in the continuous treatment period. PsARC nonresponders and patients who ceased continuous treatment transitioned to the trial period of the next treatment.

Results Ixekizumab was less costly and provided more quality-adjusted life-years (QALYs) than secukinumab in bDMARD-naïve and -experienced patients based on list prices, although cost savings and QALY gains were small to modest. In bDMARD-naïve patients, total costs were £155,455 compared with £155,530 for secukinumab (year 2017 values). Total QALYs were 8.127 versus 7.989. In bDMARD-experienced patients, the corresponding values were £140,051 versus £140,264 for total costs and 3.996 versus 3.875 for total QALYs.

Conclusion Ixekizumab provided more QALYs at a marginally lower cost than secukinumab, and the results were most sensitive to changes in drug costs. Other factors, such as patient preferences for the number of injections and confidential price discounts, may be important considerations in clinical decision-making.

Keywords Cost-effectiveness analysis · Psoriatic arthritis · Psoriasis · Ixekizumab · Secukinumab · Biologic · Sequential

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1 Introduction

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory rheumatic disease that affects $\approx 0.25\%$ of the population and is characterized by pain, stiffness, swollen joints, joint erosion, and bone formation [1, 2]. In the UK, the prevalence of psoriatic arthritis is estimated to be approximately 0.1–0.3% of the population [3]. PsA commonly coexists with psoriasis [1, 2]. In particular, moderate-to-severe PsA is associated with reduced health-related quality of life and substantial healthcare resource use and costs [4–7].

Key Points for Decision Makers

This CEA compares ixekizumab and secukinumab in PsA in the UK; this comparison to secukinumab was considered particularly relevant in a decision-making context (i.e. they have the same mechanism of action and are both recommended by NICE under similar conditions of use).

In both bDMARD-naïve and -experienced patients with PsA and concomitant moderate-to-severe psoriasis, ixekizumab provided more QALYs at a lower cost than secukinumab.

Although gains with ixekizumab were modest, the findings of this CEA, along with patient preferences and other factors, may be helpful in clinical decision-making.

Several biologic disease-modifying antirheumatic drugs (bDMARDs) are approved for treating patients with PsA. bDMARDs are major drivers of total costs in the management of PsA [6, 8]; for example, they accounted for approximately 70% of the total direct cost of PsA in a large US cohort [8]. The use of bDMARDs in the UK is under increasing scrutiny, especially given the advent of biosimilars and the growing number of biologic agents. Among the interleukin (IL) antagonists that are reimbursed in the UK, the most recently introduced agent is ixekizumab, a high-affinity monoclonal antibody that selectively targets IL-17A, a proinflammatory cytokine implicated in the pathogenesis of psoriatic arthritis [1, 9]. Secukinumab, another IL-17A antagonist, is among the most recently approved bDMARDs for PsA, and is indicated at a dosage of 300 mg (at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing) for patients with concomitant moderate-to-severe psoriasis [10].

To address the lack of published cost-effectiveness analyses (CEAs) of ixekizumab in PsA in the UK, we conducted a CEA from the perspective of the UK National Health Service (NHS) using an adaptation of the economic framework of the most recent version of the York model, as the York model and updated versions of it are considered the ‘gold standard’ in this setting [11–13]. We aimed to assess the cost-effectiveness of ixekizumab versus secukinumab in patients with PsA and concomitant moderate-to-severe plaque psoriasis. Secukinumab was selected as a comparator because both agents have similar mechanisms of action and have demonstrated efficacy in PsA and plaque psoriasis [9, 10], so decision-makers may wish to select between these IL-17A antagonists. In addition, both drugs are recommended by NICE in the UK under similar conditions of use in the treatment of patients with active PsA after conventional DMARDs [14, 15].

2 Methods

2.1 Model Overview

A Markov model was developed to compare the cost-effectiveness of ixekizumab versus secukinumab in a hypothetical cohort of adult patients with active PsA and concomitant moderate-to-severe plaque psoriasis in the UK, although the model can also be adapted for use in other countries. The model used a framework similar to that of the York model developed by Woolacott et al. [11], which has been widely used and is accepted as being relevant to PsA by NICE in the UK [12, 13]. Specifically, the model structure is closely aligned with that of the most recent version of the York model, which was used to evaluate the cost-effectiveness of various bDMARDs in patients with PsA and allowed further classification according to the level of concomitant psoriasis [13]. Like the York model, our model facilitates the analysis of treatment sequences, but it also allows for the application of a composite response criterion, so that treatment success can be evaluated based on both joint and skin symptoms (Table S1 in the Electronic supplementary material, ESM). The model includes four health states: bDMARD trial period, continuous bDMARD treatment, best supportive care (BSC) and death. The analysis used a lifetime horizon in the base case, in line with previous models [12, 13, 16–19]. The model incorporated mortality data for the normal UK population [20] adjusted for an increased disease-specific mortality risk [21] regardless of whether patients respond to treatment.

2.2 Treatment Sequences

The treatment sequences evaluated in the model were ixekizumab followed by ustekinumab then BSC versus secukinumab followed by ustekinumab then BSC in bDMARD-naïve patients, and ixekizumab followed by BSC versus secukinumab followed by BSC in bDMARD-experienced patients. The treatment sequence approach is reflective of clinical practice in the UK with potential variation in bDMARD treatment algorithms [22, 23]. Dosage regimens for all agents were as per European Medicines Agency labelling (Table 1). The trial period reflected the treatment continuation rule for therapies recommended by NICE in England and Wales, and was 16 weeks for ixekizumab and secukinumab and 24 weeks for ustekinumab. The model used monthly cycles. No half-cycle correction was applied because the cycle length was deemed sufficiently short compared to the length of the time horizon [24–26].

At the end of the trial period with initial bDMARD treatment, Psoriatic Arthritis Response Criteria (PsARC) responders transitioned to continuous treatment on the same drug and were assumed to maintain the same level of

Table 1 Treatment sequences and dosage regimens (all interleukin antagonists were administered subcutaneously)

First-line treatment	Second-line treatment	Third-line treatment
<i>bDMARD-naïve patients</i>		
Ixekizumab 80 mg Q2W/ Q4W ^a	Ustekinumab 45 mg Q12W ^b	BSC
Secukinumab 300 mg monthly ^c	Ustekinumab as above	BSC
<i>bDMARD-experienced patients^d</i>		
Ixekizumab 80 mg Q2W/ Q4W	BSC	
Secukinumab 300 mg monthly	BSC	

bDMARD biologic disease-modifying antirheumatic drug, *BSC* best supportive care, *QxW* every *x* weeks; *SC* subcutaneously, *TNF* tumour necrosis factor

^aIxekizumab regimen specifically for patients with PsA and concomitant moderate-to-severe plaque psoriasis; an initial loading dose of 160 mg is administered at week 0, followed by an 80 mg dose at weeks 2, 4, 6, 8, 10 and 12, and thereafter Q4W

^bUstekinumab 45 mg SC at week 0 and 4, then 45 mg SC Q12W in patients with body weight < 100 kg. In patients with body weight > 100 kg, the license states that the 90 mg dose may be used. No relevant clinical data pertaining to the 90 mg dose were identified that could inform the evidence syntheses; therefore, only the 45 mg dose was considered in the analyses. In the UK, ustekinumab 90 mg is recommended for use by NICE under a patient access scheme in which it is supplied by the manufacturer at the same cost as the 45 mg dose [46]

^cSecukinumab regimen specifically for patients with PsA and concomitant psoriasis or inadequate response to TNF inhibitors; an initial loading dose of 300 mg was administered at week 0, followed by a 300 mg dose at weeks 1, 2, 3 and 4, and thereafter 300 mg monthly

^dDosage regimens as for bDMARD-naïve patients

response until discontinuation. PsARC response is based on improvement from baseline in two of the following four criteria (one of which must be a joint count) without worsening in any measure: tender/swollen joints and physician/patient global assessment of disease severity [27, 28]. PsARC non-responders and patients who ceased continuous therapy transitioned to the trial period of the next bDMARD treatment or BSC if they discontinued the last treatment in the sequence. An annual all-cause discontinuation rate of 16.5% was assumed for bDMARD continuous therapy, in accordance with previous models and consistent with recent NICE submissions [12, 13]. In the absence of drug-specific data, this discontinuation rate was applied uniformly across all bDMARD comparators and treatment lines and assumed to be independent of Health Assessment Questionnaire (HAQ) and Psoriasis Area and Severity Index (PASI) scores. In patients with PsA, the HAQ is commonly used to assess physical function, and focuses on physical disability and

pain [29, 30]. PASI is a measurement of disease severity based on psoriasis symptoms. In the bDMARD-naïve subgroup, following nonresponse to or discontinuation of the last (i.e. second) bDMARD, patients transitioned to BSC (Fig. 1). In the bDMARD-experienced subgroup, patients transitioned to BSC after nonresponse to or discontinuation of the first (i.e. only) bDMARD in the treatment sequence. Patients could transition to death from any health state.

2.3 Alternative Response Criteria

As an alternative to the PsARC response criterion, the model also allows the use of a composite response criterion that combines the PsARC and PASI criteria, thereby capturing both joint and skin response in patients with PsA (Fig. 2). Although treatment decisions will likely be based predominantly on joint response in most clinical settings, it is noteworthy that NICE guidance suggests that patients whose disease has a PASI75 response ($\geq 75\%$ reduction in baseline PASI) but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate based on skin response [15]. Skin response might also play a greater role in combined dermatology/rheumatology clinics. The IL-17A antagonists and other recent bDMARDs have demonstrated robust efficacy with respect to PASI (in addition to PsARC) in PsA [13, 31–33]. While the model allows different levels of PASI response to be used (at least a 75%, 90% or 100% reduction in baseline PASI; i.e. PASI75, PASI90 or PASI100) as part of the composite response assessment, the presented analyses use PsARC and PASI75 to reflect the respective NICE recommendation [15]. The model was programmed in Visual Basic for Applications and had a Microsoft® Excel-based user interface.

2.4 Target Population

The target population was patients with active PsA and concomitant moderate-to-severe psoriasis, defined as $\geq 3\%$ of body surface area and PASI > 10. In the base-case analysis, the model incorporated demographic data that were pooled from the randomised, placebo-controlled SPIRIT-P1 and SPIRIT-P2 intent-to-treat trials (Table 2) that evaluated the efficacy of ixekizumab in bDMARD-naïve [31] and -experienced [32] patients with PsA. The model incorporates these two subpopulations based on prior therapy. EULAR guidelines note that bDMARD-experienced patients generally have lower response rates than bDMARD-naïve patients in this setting [34]. In addition, the model allows for further stratification by degree of skin involvement (no psoriasis, mild psoriasis, moderate-to-severe psoriasis); moderate-to-severe psoriasis is the focus of the current analysis.

Fig. 1 Schematic representation of the model structure in (a) bDMARD-naïve patients and (b) bDMARD-experienced patients. Although not shown in the figure, patients could transition to death from any state. BSC best supportive care, QxW every x weeks

2.5 Treatment Effect

While the response criteria (PsARC alone or PsARC and PASI) determine whether bDMARD treatment will be continued or discontinued in the model, the clinical effect of treatment is modelled as changes in baseline HAQ and PASI scores. For each bDMARD treatment, the proportion of responding patients and the magnitude of the treatment effects (i.e. changes in HAQ and PASI scores) were derived from a network meta-analysis (NMA) [35] that informed the NICE submission for ixekizumab in PsA and included data from the ixekizumab SPIRIT clinical trial programme [31, 32]. Key efficacy input data derived from the meta-analysis and used in the base-case model are provided in Table S2 of the ESM.

Generally, to account for the effect of prior treatment on the effectiveness of subsequent treatment, the first-line treatment was run using data from bDMARD-naïve patients whereas the second-line treatment used data from bDMARD-experienced patients (contingent on data availability). In all cases, improvements (i.e. reductions) in

HAQ and PASI scores were greater for responders than nonresponders. For all bDMARDs, the treatment effect was assumed to be instantaneous; therefore, utilities at the end of the trial period were applied retrospectively throughout the trial period because data are not available for earlier timepoints across treatments. Baseline HAQ and PASI scores for bDMARD-naïve and -experienced patients, stratified according to psoriasis severity, were derived from the SPIRIT clinical trial programme with ixekizumab [31, 32]. The clinical time points in the NMA were used to approximate treatment-specific time to first assessment. This trial period was 16 weeks for the IL-17 agents and 24 weeks for ustekinumab.

For responders to the chosen criteria (PsARC alone or PsARC and PASI), the initial improvement in HAQ was maintained during continuous treatment and, in the base-case analysis, reverted to baseline at discontinuation. Two alternative rebound scenarios were evaluated as sensitivity analyses: rebound to natural history (HAQ score returns to the level it would have been had the patient not responded at all to the bDMARD) and rebound to less than initial gain

Fig. 2 Model structure for the trial period when combining PsARC and PASI response criteria. *BSC* best supportive care, *PASI* Psoriasis Area and Severity Index, *PsARC* Psoriatic Arthritis Response Criteria

Table 2 Characteristics of the target patient population (patients with PsA and concomitant moderate-to-severe psoriasis) based on pooled data from the SPIRIT-P1 and SPIRIT-P2 intent-to-treat trial populations [28, 29]

Parameter	Mean value
Age	51.0 years
Proportion male	51.84%
Proportion female	48.16%
Body weight	87.0 kg
<i>bDMARD-naïve patients</i>	
Baseline HAQ score	1.19
Baseline PASI score	20.4
<i>bDMARD-experienced patients</i>	
Baseline HAQ score	1.16
Baseline PASI score	23.4

bDMARD biologic disease-modifying antirheumatic drug, *HAQ* Health Assessment Questionnaire, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis

(HAQ rebounds to 50% of initial gain, i.e. a level that is lower/better than baseline). Non-responders discontinued therapy after the trial period. In the base case, for patients who progressed to BSC, the HAQ score rebounded to the baseline HAQ level they had prior to starting the discontinued bDMARD ('rebound equal to initial gain'), although this assumption was modifiable in a sensitivity analysis. Irrespective of the rebound assumption, in the base-case analysis, patients were thereafter modelled to progress at the same rate as natural history progression (0.018 per 3-month period) until the HAQ score reached its upper bound of 3.0. This follows the same approach developed in a previous version of the York model, and is based on data from the Norfolk Arthritis Register [12].

With respect to changes in PASI scores, irrespective of the PsARC response, the model assumed there was some improvement in PASI even among PASI nonresponders if a PASI threshold of 75 or higher was chosen. For example, if

using the PsARC and PASI75 response criteria, the model allowed for some average improvement in nonresponders by taking into account the improvement in patients who reached a PASI between 50 and 75%. Conversion of relative PASI improvements to absolute levels for PASI nonresponders as well as for responders was calculated as a weighted mean of PASI response categories above or below the selected criterion according to previously applied methods [13].

If the sole response criterion PsARC is chosen, the corresponding changes in PASI scores are modelled assuming a treatment-independent correlation between PsARC and PASI response. Following a previously applied approach, a correlation coefficient of $\rho = 0.4$ was assumed for the correlation between PsARC and PASI75 [12].

When patients are on continuous treatment, the mean absolute PASI score was assumed to remain constant at the level achieved at the end of the trial period. PASI levels were assumed to return to baseline values following discontinuation of bDMARD therapy. Patients in the BSC state were assumed to achieve the same level of PASI response as observed in the placebo arms of the clinical trials included in the NMA [35].

2.6 Health-Related Quality of Life: Assignment of Health Utilities

Health utilities were based on HAQ and PASI scores from the SPIRIT-P1 and -P2 clinical trials [31, 32] with UK tariffs applied. Calculation of utilities followed the established methodology of mapping the three-level version of Euro-Qol-5 Dimensions (EQ-5D-3L) utilities onto HAQ and PASI scores using a parsimonious linear regression model without further covariates or interaction terms [13]. Alternative coefficients based on a similar algorithm that used different data were applied in a sensitivity analysis. Utilities were calculated in each model cycle by multiplying HAQ and PASI levels by the estimated regression coefficients.

2.7 Resource Use and Costs

Only direct medical costs were included in the model, as the analysis was conducted from the perspective of the NHS in the UK. Resource use associated with subcutaneous bDMARDs during the trial and continuous treatment periods included physician visits, injection training and monitoring (Table 3). Resource use estimates were derived from relevant technology appraisals [13, 36] and are in line with guidelines from the British Society for Rheumatology for the use of bDMARDs [37]. Thus, resource-use assumptions are in line with prior modelling and are reflective of clinical practice.

Table 4 provides drug acquisition costs (year 2017 values) and costs of physician visits, injection training and

Table 3 Resource use for subcutaneous bDMARDs (adapted from [13]) during the trial period and annual resource use during the continuous treatment period

Resource	Trial period	Continuous treatment period (annually)
Rheumatologist visit	2	0
Injection training	1	0
Monitoring		
FBC	2	2
LFT	2	2
U&E	2	2
ESR	2	2
Chest X-ray	1	0
TB Heaf test	1	0
ANA test	1	0
ds DNA test	1	0

ANA antinuclear antibody, bDMARD biologic disease-modifying anti-rheumatic drug, ds double-stranded, ESR erythrocyte sedimentation rate, FBC full blood count, LFT liver function tests, TB tuberculosis, U&E urea and electrolytes

monitoring (inflated to 2015–2016 prices using the Personal Social Services Research Unit inflation index [38] where necessary).

The severity of arthritis and psoriasis can have an impact on healthcare costs in patients with PsA [13]. Therefore, in addition to the resource use and costs associated with treatment, costs related to health states measured with HAQ and PASI were included for each cycle in the model. These costs were based on algorithms that provided estimates of direct costs based on absolute HAQ and PASI scores in the modelled cohort, and included hospitalisations, surgical interventions, ambulatory and community care, and rheumatoid arthritis medication [12, 39]. PsA patients with moderate-to-severe psoriasis whose psoriasis was controlled (PASI75) had lower estimated annual costs than their counterparts whose psoriasis was not controlled (£72 vs £2,552). In addition, based on an earlier estimate that conventional DMARDs account for 15% of the direct costs [39], an adjustment factor of 0.85 was applied to bDMARD costs to avoid potential double counting with other acquisition costs that were applied separately in the model.

For patients in the BSC health state, the only costs applied were those related to HAQ and PASI without applying an adjustment factor. For those receiving bDMARD therapy during the trial or continuous treatment periods, costs associated with serious adverse events requiring hospitalisation were not included in the base-case analysis because of limited data regarding the incidence of such events for some bDMARDs and an expected relatively small contribution to overall costs and outcomes. All costs and benefits were

Table 4 Unit costs for drug acquisition, physician visits, injection training and monitoring of subcutaneous bDMARDs

Resource	Cost ^a	Source
<i>Drug acquisition costs (list prices)</i>		
Ixekizumab 80 mg prefilled pen or syringe	£1,125 per dose	MIMS (2017) [47]
Secukinumab 300 mg prefilled pen or syringe	£1,218.78 per dose	MIMS (2017) [47]
Ustekinumab 45 mg prefilled syringe	£2,147.00 per dose	MIMS (2017) [47]
Ustekinumab 90 mg prefilled syringe	£2,147.00 per dose	MIMS (2017) [47]
<i>Physician, injection training and monitoring costs</i>		
Rheumatologist visit	£142.74	DoH (2016) [48]
Injection training (1 h)	£43.00	PSSRU (2016) [38]
FBC	£3.00	DoH (2016) [48]
LFT	£1.00	DoH (2016) [48]
U&E	£1.00	DoH (2016) [48]
ESR	£3.00	DoH (2016) [48]
Chest X-ray	£30.00	DoH (2016) [48]
TB Heaf test	£8.91	Rodgers et al. (2011) [12]
ANA test	£3.00	DoH (2016) [48]
ds DNA test	£3.00	DoH (2016) [48]

ANA antinuclear antibody, bDMARD biologic disease-modifying antirheumatic drug, DoH Department of Health (NHS reference cost), ds double-stranded, ESR erythrocyte sedimentation rate, FBC full blood count, LFT liver function tests, MIMS Monthly Index of Medical Specialties, PSSRU Personal Social Services Research Unit, TB tuberculosis, U&E urea and electrolytes

^aDrug acquisition costs for the year 2017. Unit costs for physician visits, injection training and monitoring were based on the latest reference cost schedule in place (2015–2016) or were inflated to 2015–2016 prices using the Personal Social Services Research Unit inflation index where necessary

discounted at an annual rate of 3.5% as per the NICE reference case [40].

2.8 Sensitivity Analyses

Sensitivity analyses were undertaken to explore the inherent uncertainty in the base-case analysis, which incorporated various assumptions and data from several different sources. These analyses included one-way (deterministic) sensitivity analyses, a probabilistic sensitivity analysis and scenario analyses. In the one-way sensitivity analysis, where one variable was altered at a time to assess the effect on results, most input parameters were varied by $\pm 20\%$ of the mean value, as 95% confidence interval (CI) values were not available. Notable exceptions were ranges of values used for the efficacy of bDMARDs and BSC ($\pm 10\%$ of mean values from the NMA), the annual discontinuation rate (95% CI), the discount rate for costs and health utilities (1.5%, 6%), and physician and monitoring costs (± 1 visit or test).

In addition, a probabilistic sensitivity analysis was conducted by assigning distributions to input parameters and sampling from these distributions in 1000 simulations. For efficacy inputs, instead of applying parametric distributions, the CODA (Convergence Diagnostics and Output Analysis) output of the Bayesian NMA was used [35, 41]. A beta distribution was used for values that ranged between 0 and 1, and a gamma distribution was assumed for all other

parameters that ranged between zero and infinity. Input parameters for this analysis included PsARC and PASI response rates, baseline HAQ and PASI, withdrawal rates, changes in HAQ and health utility, mortality and various costs. The scenario analysis included alternative inputs for health state costs, HAQ rebound options, the EQ-5D utility algorithm, the definition of response (i.e. combined criteria of PsARC and either PASI75, PASI90 or PASI100) and an analysis of subgroups with less severe or no psoriasis.

3 Results

In the base-case analysis in patients with PsA and concomitant moderate-to-severe psoriasis, ixekizumab was associated with lower total costs and higher total quality-adjusted life-years (QALYs) than secukinumab in both bDMARD-naïve and bDMARD-experienced patients. Although ixekizumab was dominant in both subpopulations, cost savings and QALY gains over secukinumab were small to modest (Table 5). In bDMARD-naïve patients treated with ixekizumab followed by ustekinumab then BSC, total costs over the lifetime horizon of the model were £155,455, as compared with £155,530 for secukinumab followed by ustekinumab then BSC (year 2017 values). Total QALYs were also generally similar for both sequences, although they favoured ixekizumab (8.127

Table 5 Results of the base-case analysis

Parameter	bDMARD-naïve patients		Difference	bDMARD-experienced patients		Difference
	Ixekizumab	Secukinumab		Ixekizumab	Secukinumab	
Total costs	£155,455	£155,530	– £75	£140,051	£140,264	– £213
Total QALYs	8.127	7.989	+ 0.138	3.996	3.875	+ 0.121
ICER	Dominant			Dominant		

bDMARD biologic disease-modifying antirheumatic drug, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-years

vs 7.989). In bDMARD-experienced patients, the corresponding values for ixekizumab followed by BSC compared with secukinumab followed by BSC were £140,051 versus £140,264 for total costs and 3.996 versus 3.875 for total QALYs.

One-way sensitivity analysis in bDMARD-naïve patients showed that base-case results were generally robust to changes in most input parameters with the exception of IL-17A antagonist costs and PsARC response (Fig. 3a). Results were also sensitive to a modification of PsARC response by $\pm 10\%$ for the IL-17A antagonists, although not to the same extent as costs (Fig. 3a). Results of the one-way sensitivity analysis in bDMARD-experienced patients were generally similar to those in bDMARD-naïve patients in that the base-case results were robust to modifications of most input parameters but were sensitive to changes in ixekizumab and secukinumab costs and PsARC response (Fig. 3b).

Probabilistic sensitivity analysis for bDMARD-naïve patients showed that almost one-third (31.3%) of the observations were in the southeast quadrant of the cost-effectiveness plane, indicating that ixekizumab was less costly and provided more QALYs than secukinumab. Approximately half (46.8%) of the observations were in the northeast quadrant, indicating that ixekizumab was more costly than secukinumab but provided more QALYs. Base-case results were under a willingness-to-pay (WTP) threshold of £20,000 per QALY gained (Fig. 4a). For bDMARD-experienced patients, 20.7% and 47.1% of the observations were in the southeast and northeast quadrants, respectively, and base-case results were also under a WTP threshold of £20,000 per QALY gained (Fig. 4b).

The cost-effectiveness acceptability curve for bDMARD-naïve patients showed that, compared with secukinumab, ixekizumab had a 90% probability of being cost-effective at a WTP threshold of £20,000 per QALY gained and a 96% probability at a threshold of £30,000 per QALY gained (Fig. 5a). For bDMARD-experienced patients, the respective probabilities were 85% and 82% (Fig. 5b).

In the scenario analyses where different HAQ rebound options were evaluated, ixekizumab continued to dominate secukinumab regardless of the HAQ rebound scenario in

bDMARD-naïve and -experienced patients. For almost all other scenarios evaluated (see Sect. 2.8), ixekizumab was less costly and provided more QALYs than secukinumab or was associated with an incremental cost-effectiveness ratio (ICER) under a WTP threshold of £30,000 per QALY gained for bDMARD-naïve and -experienced patients (Table S3 in the ESM). The only exceptions were in bDMARD-naïve PsA patients with no concomitant psoriasis or mild-to-moderate concomitant psoriasis, where secukinumab provided small advantages in QALYs gained but was associated with higher costs, resulting in ICERs > £175,000 per QALY gained for secukinumab versus ixekizumab.

4 Discussion

This CEA compared the IL-17A antagonists ixekizumab and secukinumab in the management of patients with PsA and concomitant moderate-to-severe plaque psoriasis in the UK. Results of the base-case analysis showed that ixekizumab was associated with lower total costs and higher total QALYs than secukinumab in both bDMARD-naïve and bDMARD-experienced patients, although differences were small to modest. Secukinumab was selected as the comparator in the analysis because decision-makers may wish to select between ixekizumab and secukinumab in view of their shared mechanism of action and since both were reviewed and recommended by NICE with similar conditions of use [14, 15].

Our model allows for treatment sequencing (of up to four active treatments) as well as pairwise comparisons. As noted previously, a treatment sequencing approach is reflective of clinical practice in the UK. In addition, there may be costs and benefits associated with the end of a treatment sequence that are only apparent if a sequence is modelled. For example, as BSC is associated with poorer clinical outcomes than active treatments, upstream treatments that reduce the duration of treatment with BSC will be associated with a greater QALY improvement. Modelling treatment sequences may therefore be important to reflect the decision problem accurately.

Fig. 3 Results of one-way sensitivity analyses in (a) bDMARD-naïve and (b) bDMARD-experienced patients. *Admin* administration, *bDMARD* biologic disease-modifying antirheumatic drug, *HAQ* Health Assessment Questionnaire, *ICER* incremental cost-effective-

ness ratio, *Ixe* ixekizumab, *PASI* Psoriasis Area and Severity Index, *PsARC* Psoriatic Arthritis Response Criteria, *QALY* quality-adjusted life-year, *QxW* every *x* weeks, *Sec* secukinumab, *Trt* treatment, *Ust* ustekinumab

The model also allows for the combination of PsARC and PASI as a response criterion, thereby capturing both joint and skin responses in patients with PsA. This may be particularly useful when evaluating clinical benefits of newer-generation bDMARDs, such as IL-17A antagonists in PsA [42, 43]. The model also has a relatively short cycle length of 1 month, thereby allowing for differential lengths of the trial period for different treatments, and uses ixekizumab trial-based utility equations. In addition, it is a global model that can be adapted for use in other countries where reimbursement and possibly treatment options/sequences may differ from those in the UK.

In the context of PsA and findings from meta-analyses and long-term registry data in the UK [12, 44], it is reasonable to

assume that transition probabilities for treatment discontinuation beyond the initial induction period (e.g. due to loss of efficacy or treatment intolerance) are constant rather than dependent on identifiable events; therefore, PsA is a disease that is generally well suited to the memoryless nature of a Markov model framework.

Several health economic analyses have been conducted in the treatment of PsA, as highlighted in a recent systematic review [6], and findings of two recent analyses are noteworthy. A Canadian CEA reported that secukinumab either dominated or was cost-effective when compared with all other licensed bDMARDs in treating active PsA in bDMARD-naïve and -experienced populations [45]. However, ixekizumab was not included in the analysis. In

A

Scatter plot Ixe Q2W/Q4W - Ust vs Sec 300mg - Ust

B

Scatter plot Ixe Q2W/Q4W vs Sec 300mg

Fig. 4 Results of probabilistic sensitivity analyses in (a) bDMARD-naïve and (b) bDMARD-experienced patients. *bDMARD* biologic disease-modifying antirheumatic drug, *Ixe* ixekizumab, *QALY* quality-adjusted life-year, *QxW* every *x* weeks, *Sec* secukinumab, *Ust* ustekinumab, *WTP* willingness to pay

the UK, a systematic review and CEA evaluated the cost-effectiveness of secukinumab and certolizumab pegol versus other relevant comparators for treating active PsA following

an inadequate response to DMARDs [13]. Results indicated that both of these agents may be an effective use of NHS resources depending on the subpopulation and psoriasis severity, although an important study limitation was data availability.

Data availability was also a limitation of our analysis, as some of the underlying data (e.g. cost estimates for health states) were based on relatively old studies and/or conducted

Fig. 5 Cost-effectiveness acceptability curves for (a) bDMARD-naïve and (b) bDMARD-experienced patients. *bDMARD* biologic disease-modifying antirheumatic drug, *Ixe* ixekizumab, *QxW* every *x* weeks, *Sec* secukinumab, *Ust* ustekinumab, *WTP* willingness to pay

in rheumatoid arthritis patients (e.g. [39]). However, these sources are still used in assessments of bDMARDs for the treatment of PsA [12, 13, 16–19], as the ability to carry out similar research has been hindered by a lack of respective PsA cohorts to date, highlighting a potential area for further research. There is also, generally, a lack of underlying data on treatments constituting BSC and their efficacies. Also, as noted in Sect. 2.5, responses/utilities at the end of the trial period were applied retrospectively throughout the trial period because data are not available for earlier timepoints across treatments.

Another possible limitation of our analysis is that it used list prices for drugs rather than confidential, preferentially priced patient access scheme costs in the UK. In addition, other factors that might drive treatment decisions (e.g. patient preference for the number of injections, injection device design or availability of longer-term safety data) were not included in the model. Also, the model relied on efficacy input data from a NMA, as there were no head-to-head comparative trials between ixekizumab and secukinumab or other bDMARDs in PsA in general, or in patients with PsA and concomitant moderate-to-severe psoriasis, which was the target population in our analysis. Nevertheless, one of the main findings of the NMA was that there were generally few statistically significant differences between most treatments [35].

There is also uncertainty regarding the annual discontinuation rate of 16.5% that was used in the base-case analysis. Although this was in accordance with previous models and with NICE submissions [12, 13], further research is warranted. In addition, while we did not employ any of the standard checklists for model validity, we have carried out a thorough test of the functionality, and the model has been extensively validated by an external health outcomes expert.

Although total costs and QALYs were quite similar for ixekizumab and secukinumab, with a modest advantage to ixekizumab for both parameters in bDMARD-naïve and -experienced patients with PsA and concomitant moderate-to-severe psoriasis, we believe the findings of our analysis still provide insights that may be helpful for healthcare decision-makers when allocating resources.

5 Conclusion

Findings of this cost-effectiveness analysis in patients with PsA and concomitant moderate-to-severe psoriasis in the UK showed that, when list prices were used, ixekizumab provided more QALYs at a lower cost than secukinumab in both bDMARD-naïve and -experienced patients, although the total cost and QALY differences were small and the base-case results were most sensitive to changes in costs for these IL-17A antagonists. Results were generally robust

to modifications of most other input parameters. In light of the relatively small magnitudes of cost and QALY differences, other factors not included in our model, such as patient preferences for number of injections and confidential price discounts, may be important to consider in clinical decision-making.

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Data Availability All data relevant to the study are included in the article or uploaded as supplementary information. Eli Lilly and Company Ltd may be able to consider sharing the executable model upon request, at which point a case-by-case judgement would be made to ensure adherence to company procedures. The executable CEA model is proprietary material and any request will need to be carefully considered.

Compliance with Ethical Standards

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Conflicts of Interest BS, CM and ÖÅ are full-time employees of ICON who were commissioned by Eli Lilly and Company to conduct the analysis for this work. GK, CS and SH are full-time employees of Eli Lilly and Company, receive a salary, and own company stock. DN and SK were full-time employees of Eli Lilly and Company during the inception of the work.

Statement of Human Rights and Animal Welfare This article does not contain any studies with human participants or animals performed by any of the authors.

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