RHEUMATOLOGY

Rheumatology 2021;60:4367–4372
doi:10.1093/rheumatology/keaa824
Advance Access publication 20 January 2021

Concise report

Improvement from ixekizumab treatment in patients with psoriatic arthritis who have had an inadequate response to one or two TNF inhibitors

Bruce Kirkham[1], Carlos Sesin[2], Amanda M. Gellett[3], Aubrey T. Sprabery[3], Chen-Yen Lin[3] and Anthony Turkiewicz[4]

Abstract

Objective. To evaluate the efficacy of ixekizumab (IXE), a monoclonal antibody selectively targeting interleukin-17A, in patients with inadequate response to one or two TNF inhibitors (TNFi).

Methods. A phase 3 study (SPIRIT-P2; NCT02349295) randomized patients with PsA with inadequate response or intolerance to one or two TNFi to receive 80-mg IXE every 2 weeks ($n = 123$) or every 4 weeks ($n = 122$) after a 160-mg starting dose or placebo (PBO; $n = 118$) through week 24. This *post hoc* analysis used data from inadequate responders to one or two TNFi, measuring the percentage achieving: $\geq$50% improvement in ACR response criteria (ACR50) and 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI 100), ACR50, improvement in HAQ-Disability Index (HAQ-DI) $\geq$0.35, minimal disease activity (MDA), European League Against Rheumatism (EULAR) Good Response Criteria [improvement in Disease Activity Score 28 CRP (DAS28-CRP) $>$1.2], and Disease Activity in PsA (DAPSA) $\leq$14.

Results. There were no significant differences in baseline characteristics between inadequate responders to one and two TNFi. At week 24, significantly more patients irrespective of previous TNFi experience receiving IXE than PBO achieved ACR50, HAQ-DI $\geq$0.35 improvement, MDA, EULAR good response, and DAPSA $\leq$14, and significantly more patients with inadequate response to one TNFi receiving IXE than PBO achieved ACR50 and PASI 100. Improvement persisted in all measures through week 52.

Conclusion. IXE improved the signs and symptoms of PsA in a population of difficult-to-treat patients with inadequate response to one or two TNFi.

Key words: psoriatic arthritis, tumour necrosis factor inhibitor, inadequate responders, interleukin-17A, ACR, HAQ-DI, DAPSA

CLINICAL SCIENCE

Rheumatology key messages

- Patients with PsA with failed response to TNFi present a specific challenge to rheumatologists.
- Ixekizumab is effective for patients with PsA who have failed response to a TNFi.

Introduction

PsA is a chronic inflammatory disease that affects the joints, periarticular structures, skin and nails [1]. Treatment guidelines for PsA generally recommend TNF inhibitors (TNFi) as the first-line biologic disease-modifying antirheumatic drug (bDMARD) [2, 3]. Although TNFi are efficacious in treating the signs and symptoms of PsA, not all patients respond to TNFi, and over time, many lose response [4]. At one year, rates of drug survival for first-line TNFi have been reported at values ranging from 46% to 84%; two-year rates of survival for first-line TNFi have been reported at values ranging from 52% to 75% [5]. Patients who switch to a second TNFi have worse responses than those who do not switch, and drug survival for a second-line TNFi is lower than for first-line TNFi [5]. Treatments with different mechanisms of action may be an option for patients with PsA who have failed one or more TNFi.

[1]Guy's & St Thomas' NHS Foundation Trust, London, UK, [2]Mount Sinai Medical Center, Miami Beach, FL, [3]Eli Lilly and Company, Indianapolis, IN and [4]Rheumatology Associates, Birmingham, AL, USA

Submitted 1 July 2020; accepted 28 October 2020

Correspondence to: Bruce Kirkham, Guy's & St Thomas' NHS Foundation Trust, London, UK. E-mail: bruce.kirkham@gstt.nhs.uk

Ixekizumab (IXE), a high-affinity monoclonal antibody that selectively targets interleukin-17A, is approved for treating active PsA, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and moderate-to-severe plaque psoriasis [6]. IXE has shown efficacy in patients with PsA who are naive to bDMARD (SPIRIT-P1) and in those with an inadequate response or intolerance to TNFi (SPIRIT-P2) [7, 8]. In this *post hoc* subgroup analysis of SPIRIT-P2, we aimed to assess the efficacy of IXE in patients with inadequate response to one or two TNFi.

Methods

Study design

SPIRIT-P2 (NCT02349295; EudraCT 2011–002328-42) is a randomized, double-blind, placebo (PBO)-controlled phase 3 study in patients with active PsA and a previous inadequate response or intolerance to one or two TNFi. Detailed methodology has been published [8]. Briefly, patients were randomized 1:1:1 to subcutaneous administration of PBO or either 80-mg ixekizumab every 4 weeks (IXE Q4W) or 2 weeks (IXE Q2W) following a 160-mg starting dose at week 0. At week 16, inadequate responders [defined by blinded, predefined criteria of $<$20% improvement from baseline in both tender joint count (TJC) and swollen joint count (SJC)] were required to add or modify concomitant medications. At week 24, patients in the PBO group were re-randomized to IXE Q2W or IXE Q4W through the remainder of the study, and patients in the IXE group remained on their original dose. At week 32 and any subsequent visit, patients were discontinued if they did not achieve $\geq$20% improvement from baseline in both TJC and SJC. These *post hoc* data were derived from patients in the intent-to-treat (ITT) population with prior inadequate response to one or two TNFi; patients who were intolerant to TNFi were excluded from the analysis.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Bellberry Human Research Ethics Committee (Application #2015–01-049-AA). Patients provided written informed consent before the study-related procedures were performed.

Study population

Detailed eligibility criteria have been published [8]. Briefly, enrolled adult patients were male or female who met the Classification Criteria for PsA (CASPAR), had active PsA (defined as the presence of $\geq$3 TJC and $\geq$3 SJC) and active psoriatic skin lesion or a documented history of plaque psoriasis. Patients were previously treated with TNFi and had to have an inadequate response or intolerance to one or two TNFi.

Assessments

Efficacy outcome measurements for this *post hoc* analysis included percentage of patients who attained simultaneous $\geq$50% improvement in ACR response criteria (ACR50) and 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI 100), ACR50, improvement in HAQ-Disability Index (HAQ-DI) $\geq$0.35 (minimal clinically important difference), minimal disease activity (MDA), European League Against Rheumatism (EULAR) Good Response Criteria [an absolute of $\leq$3.2 and improvement in Disease Activity Score 28–CRP (DAS28-CRP) $>$1.2], and Disease Activity in PsA (DAPSA) $\leq$14.

Statistical methods

All analyses were performed on the ITT population (defined as all patients randomized at week 0) stratified by previous TNFi experience, except for the simultaneous ACR50 and PASI100 where a subset of patients with baseline BSA $\geq$ 3% was used. Patients who were intolerant to TNFi were excluded from the analysis. Treatment comparisons between IXE and PBO up to week 24 were conducted using Fisher's exact test. Missing values were imputed by non-responder imputation. Inadequate responders at week 16 were analysed as non-responders at weeks 20 and 24. Descriptive statistics were reported up to week 52 for patients initially randomized to either dose of IXE.

Results

In SPIRIT-P2, about 90% (332) patients had discontinued prior TNFi therapy due to an inadequate response, with 204 and 128 patients having inadequate response to one and two TNFi, respectively; the remainder of patients (31) were intolerant to TNFi and excluded from this *post hoc* analysis. Among the patients included in this analysis, the baseline demographics and disease characteristics were not significantly different between those who had an inadequate response to one TNFi (one-TNFi-IR) and those with an inadequate response to two TNFi (two-TNFi-IR). There were fewer males in the PBO and IXE Q2W groups among those patients who failed two-TNFi compared with those who failed one TNFi. On average, the time since PsA diagnosis was one to two years longer in patients who failed two TNFi than patients who failed only one TNFi. Patients in the two-TNFi-IR group on average had higher joint count than those in the one-TNFi-IR group (TJC: 25.0 *vs* 22.2; SJC: 13.1 *vs* 11.9). Among the two-TNFi-IR, patients randomized to IXE Q2W had the highest TJC and SJC ($\sim$29 and 16, respectively). About 50% of the patients remained on concomitant background conventional synthetic DMARD therapy during the study, and most of those patients were receiving methotrexate. The most common prior TNFi across all study groups was adalimumab or etanercept. About 25% of two-TNFi-IR patients had also received infliximab. Golimumab and certolizumab were used less frequently across both subgroups (Table 1).

Table 1 Baseline demographics and disease characteristics, ITT population

	Inadequate responders to 1 TNFi			Inadequate responders to 2 TNFi		
	PBO ($n = 68$)	IXE Q4W ($n = 71$)	IXE Q2W ($n = 65$)	PBO ($n = 41$)	IXE Q4W ($n = 41$)	IXE Q2W ($n = 46$)
Age (years)	51.6 (9.6)	52.5 (14.1)	50.8 (11.8)	51.4 (12.0)	52.0 (12.7)	53.0 (12.2)
Male, *n* (%)	36 (52.9)	37 (52.1)	30 (46.2)	15 (36.6)	21 (51.2)	18 (39.1)
Time since PsA diagnosis (years)	9.6 (7.7)	10.9 (10.3)	9.3 (7.5)	8.8 (7.2)	11.9 (9.2)	11.2 (7.4)
TJC (68 joints)	21.3 (17.0)	22.3 (14.1)	23.1 (16.9)	23.9 (13.4)	22.0 (13.9)	28.8 (18.3)
SJC (66 joints)	10.1 (7.4)	13.0 (11.3)	12.5 (9.6)	10.1 (7.6)	13.0 (9.6)	15.7 (14.5)
CRP (mg/l)[a]	9.8 (15.6)	16.0 (26.4)	17.1 (30.3)	16.0 (25.6)	17.1 (27.6)	10.4 (22.1)
HAQ-DI[b]	1.1 (0.7)	1.2 (0.6)	1.2 (0.7)	1.4 (0.7)	1.2 (0.6)	1.3 (0.6)
DAS28-CRP[b]	4.9 (1.2)	5.1 (1.1)	5.1 (1.1)	5.1 (1.0)	5.1 (1.0)	5.3 (1.1)
DAPSA score[c]	45.5 (24.1)	50.1 (22.4)	51.5 (26.9)	48.1 (19.2)	50.4 (19.0)	58.7 (31.2)
Background cDMARD therapy						
Current use of cDMARD, *n* (%)	32 (47.1)	37 (52.1)	37 (56.9)	17 (41.5)	19 (46.3)	28 (60.9)
Current use of MTX, *n* (%)	23 (33.8)	28 (39.4)	30 (46.2)	14 (34.1)	16 (39.0)	24 (52.2)
Prior failed TNFi, *n* (%)						
Adalimumab	23 (33.8)	24 (33.8)	29 (44.6)	31 (75.6)	32 (78.0)	32 (69.6)
Certolizumab	7 (10.3)	8 (11.3)	5 (7.7)	4 (9.8)	3 (7.3)	3 (6.5)
Etanercept	30 (44.1)	24 (33.8)	24 (36.9)	30 (73.2)	30 (73.2)	32 (69.6)
Golimumab	2 (2.9)	5 (7.0)	1 (1.5)	2 (4.9)	7 (17.1)	6 (13.0)
Infliximab	6 (8.8)	10 (14.1)	6 (9.2)	11 (26.8)	9 (22.0)	14 (30.4)

Data are mean (S.D.) unless stated otherwise. [a]1 TNFi Inadequate Responders, Nx: PBO = 67, IXE Q4W = 69, IXE Q2W = 65; 2 TNFi Inadequate Responders, Nx: PBO = 40, IXE Q4W = 41, IXE Q2W = 46. [b]1 TNFi Inadequate Responders, Nx: PBO = 67, IXE Q4W = 70, IXE Q2W = 64; 2 TNFi Inadequate Responders, Nx: PBO = 41, IXE Q4W = 41, IXE Q2W = 44. [c]1 TNFi Inadequate Responders, Nx: PBO = 67, IXE Q4W = 69, IXE Q2W = 64; 2 TNFi Inadequate Responders, Nx: PBO = 41, IXE Q4W = 41, IXE Q2W = 45. cDMARD: conventional disease-modifying antirheumatic drug; DAPSA: Disease Activity in Psoriatic Arthritis; DAS28-CRP: Disease Activity Score 28–CRP; HAQ-DI: HAQ-Disability Index; ITT: intent-to-treat; IXE Q2W: 80-mg ixekizumab every 2 weeks; IXE Q4W: 80-mg ixekizumab every 4 weeks; *n*: number of patients in each subgroup; Nx: number of patients with non-missing data; PBO: placebo; SJC: swollen joint count; TJC: tender joint count; TNFi: TNF inhibitor(s).

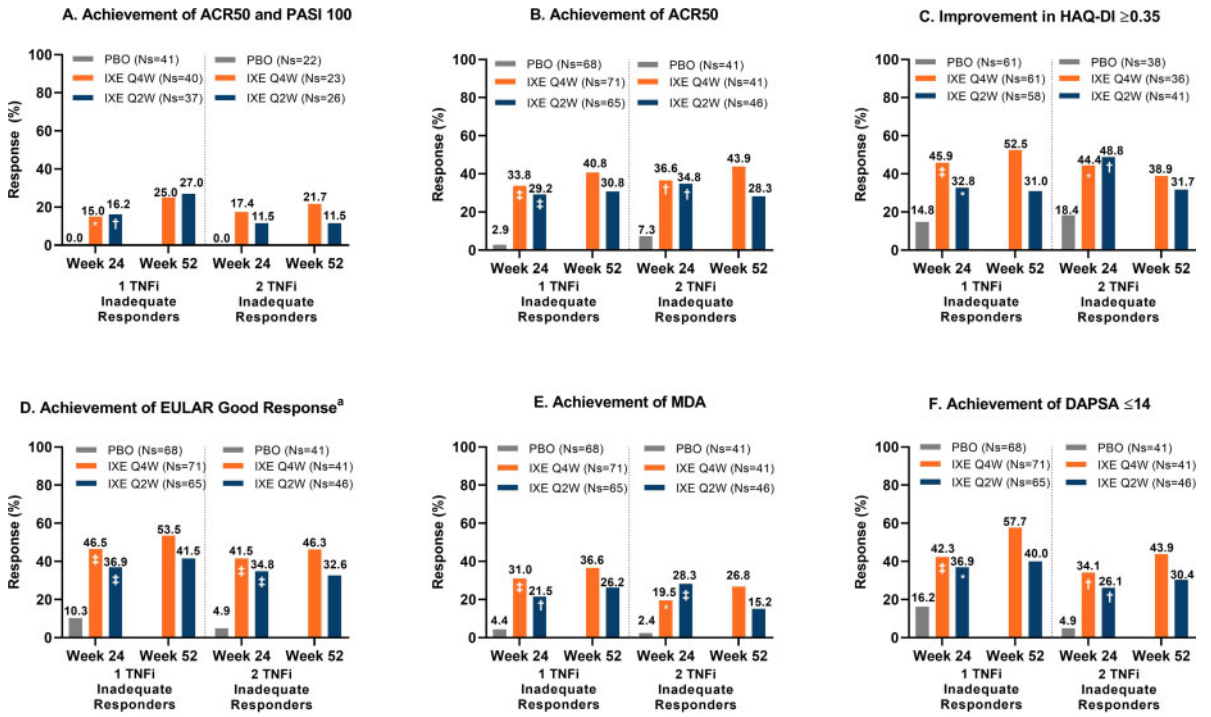
At week 24, regardless of inadequate response to one or two TNFi, significantly more patients who received IXE than PBO achieved ACR50, HAQ-DI $\geq$0.35 improvement, MDA, EULAR good response, and DAPSA $\leq$14 (Fig. 1). Further, significantly more patients who received IXE than PBO who had inadequate response to one TNFi achieved ACR50 and PASI 100 simultaneously (Fig. 1A). Additionally, the responses achieved were comparable between the subgroups. In the approved dosing regimen for patients with active PsA (IXE Q4W), 15% and 17% of patients with an inadequate response to one or two TNFi, respectively, simultaneously achieved ACR50 and PASI 100 at week 24; 34% and 37% of patients with an inadequate response to one or two TNFi, respectively, achieved ACR50 at week 24. Almost 50% of patients in both subgroups had an improvement from baseline of $\geq$0.35 in HAQ-DI (45%) and achieved a EULAR good response (44%). There were numerical differences between the one-TNFi-IR and two-TNFi-IR populations with regard to MDA and DAPSA $\leq$ 14, but both subgroups had statistically greater differences compared with PBO at week 24 (MDA in one-TNFi-IR group: IXE Q4W *vs* PBO $P < 0.001$ and IXE Q2W *vs* PBO $P < 0.01$; two-TNFi-IR group: IXE Q4W *vs* PBO $P < 0.05$ and IXE Q2W *vs* PBO $P < 0.001$; and DAPSA in one-TNFi-IR group: IXE Q4W *vs* PBO $P < 0.001$ and IXE Q2W *vs* PBO $P < 0.05$; two-TNFi-IR group: IXE Q4W *vs* PBO $P < 0.01$ and IXE Q2W *vs* PBO $P < 0.01$).

At week 52 in the IXE Q4W treatment group, 25% of one-TNFi-IR patients and 22% of two-TNFi-IR patients simultaneously achieved ACR50 and PASI 100; 41% of one-TNFi-IR patients and 44% of two-TNFi-IR patients achieved ACR50. Numerically, more one-TNFi-IR patients than two-TNFi-IR patients achieved HAQ-DI $\geq$0.35 improvement as well as the more stringent outcomes of EULAR good response, DAPSA $\leq$ 14, and MDA. Overall, responses were consistent among both subgroups across the five outcomes analysed.

Discussion

In patients who had an inadequate response or were intolerant to one or two TNFis, treatment with IXE resulted in improvements in the signs and symptoms of PsA, and these improvements persisted over 52 weeks of treatment [8, 9]. Previously, we showed that IXE provides comparable efficacy between patients who have an inadequate response to one TNFi and those with two TNFi as measured by ACR20 [8]. In this report, we

Fig. 1 Percentage of patients in ITT population



(**A**) simultaneously achieving ACR50 and PASI 100, (**B**) achieving ACR50, (**C**) achieving HAQ-DI ≥0.35, (**D**) achieving EULAR good response, (**E**) achieving MDA, and (**F**) achieving DAPSA ≤14. [a]Good Response Criteria defined as >1.2 improvement and ≤ 3.2 present DAS28-CRP.
*P <0.05, †P <0.01, ‡P <0.001 vs PBO, Fisher's exact test. ACR50: at least 50% improvement in ACR response criteria; ITT: intent-to-treat; IXE Q2W: 80-mg ixekizumab every 2 weeks; DAS28-CRP: Disease Activity score (28 diarthrodial joint count) based on CRP; HAQ-DI: HAQDisability Index; IXE Q4W: 80-mg ixekizumab every 4 weeks; MDA: minimal disease activity; Ns: number of patients in each subgroup; PASI 100: 100% improvement from baseline in the Psoriasis Area and Severity Index; PBO: placebo; TNFi: TNF inhibitor.

further investigated the effect of IXE among a subgroup of patients who had an inadequate response to one and two TNFi including more relevant clinical endpoints such as the simultaneous achievement of ACR50 and PASI 100, ACR50, HAQ-DI ≥0.35 improvement, EULAR good response, DAPSA ≤ 14, and MDA. In this subpopulation analysis of SPIRIT-P2, 61% of patients were inadequate responders to one TNFi and 39% of patients were inadequate responders to two TNFi. Patients in the IXE Q2W and IXE Q4W treatment groups achieved superior outcomes compared with those in the PBO at week 24, and the effects were sustained to week 52, regardless of a prior inadequate response to one or two TNFi. Among patients who received IXE Q4W, the approved dose of IXE for patients with PsA, one-TNFi-IR patients performed numerically better in most outcomes at 52 weeks compared with two-TNFi-IR patients, but the study was not designed to investigate statistical differences between these two groups. Additionally, there was no PBO group beyond week 24, so comparisons with long-term results could not be made. This analysis has the inherent limitations associated with a *post hoc* analysis. As we conducted this study with a subgroup of patients from SPIRIT-P2, it is difficult to assess outcomes measures that further reduce the population size, such as plaque psoriasis, enthesitis or dactylitis. Furthermore, using the study data available, it is unclear whether the patients have primary or secondary TNFi failures, which may have provided more insights around the results.

Although the 2018 ACR/National Psoriasis Foundation treatment guidelines for PsA encourage the use of a second TNFi if a patient has active disease despite receiving a TNFi, there is little evidence on the benefit of cycling TNFi in PsA [3]. These data are increasingly important because other mode-of-action therapies are now available. Several studies show that patients discontinue TNFi primarily due to lack of efficacy and have lower response rates and reduced drug survival with subsequent TNFi. One such study, from the DANBIO registry, suggested responses after one and particularly two previous TNFi therapies were poor. Their results showed that following 3–6 months of treatment, the proportion of patients on their first, second and third treatment courses who achieved ACR50 was 33%, 13% and 6%, respectively. In this analysis, about 50% of the patients switched

to a second and third biologic due to lack of effect: 57% of 548 switchers and 62% of 189 switchers, respectively [5]. The longitudinal observational NOR-DMARD study found that 1-year drug survival of a second TNFi was significantly less than that in patients staying on their first TNFi (56% *vs* 83%, respectively). This study also identified a trend towards poorer responses with the second TNFi compared with the first TNFi, with ACR50 at 3 months being achieved by 23% of 63 switchers to a second TNFi compared with 40% of 259 non-switchers ($P = 0.05$) [10]. Similarly, the US-based CORRONA PsA/Spondyloarthritis Registry identified lack of efficacy as the most common reason for discontinuation in both TNFi-naive (90%) and TNFi-experienced (73%) patients, with shorter time to discontinuation for TNFi-switch patients compared with those on their first TNFi (20 months *vs* 27 months; $P = 0.03$) [11]. Data from the British Society for Rheumatology Biologics Register and DANBIO Registry corroborate decreased drug survival time in patients on their second TNFi [5, 12].

Patients with PsA who have had an inadequate response to TNFi present specific challenges to clinicians and have not been studied extensively (particularly two TNFi) in dedicated clinical studies. This *post hoc* analysis of SPIRIT-P2 suggests that IXE is also an effective treatment option if a patient with PsA has had an inadequate response to one or two TNFi.

Conclusion

This *post hoc* analysis suggests that IXE improved the signs and symptoms of PsA in a population of difficult-to-treat patients who have had inadequate response to one or two TNFi. IXE Q2W and Q4W demonstrated improvement at week 24, which persisted among patients continuously dosed with IXE through week 52 on all the six outcomes analysed. Therefore, IXE may provide clinicians with an effective treatment option for patients with PsA who have failed one or two TNFi.

Acknowledgements

The authors would like to acknowledge Lahari N.A., M. Pharm, Eli Lilly and Company, and Nicole Lipitz, Syneos Health, for their writing support and assistance with the preparation of this manuscript. All authors participated in the interpretation of study results and in the drafting, critical revision, and approval of the final version of the manuscript.

Disclosure statement: B.K. is a consultant for AbbVie, Eli Lilly and Company, Gilead, Janssen, Novartis, and UCB, and has received research funding from AbbVie, Arthritis Research UK, Eli Lilly and Company and Novartis; C.S. has received consulting fees from Pfizer and Radius, and is a speaker for Abbvie, Amgen, Celgene, Eli Lilly and Company, Novartis, Pfizer, Radius, and Sanofi-Genzyme; A.T.S., C-Y.L. and A.M.G. are employees and shareholders of Eli Lilly and Company; A.T. has received research grants or consulting fees from AbbVie, Eli Lilly and Company, Janssen, Novartis, and Pfizer, and is on the speakers' bureau for AbbVie, Eli Lilly and Company, Janssen, Novartis, and Pfizer.

Funding: This work was supported by Eli Lilly and Company.

Data availability statement

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

References

1 Eder L, Gladman DD. Psoriatic arthritis: phenotypic variance and nosology. Curr Rheumatol Rep 2013;15:316.

2 Merola JF, Lockshin B, Mody EA. Switching biologics in the treatment of psoriatic arthritis. Semin Arthritis Rheum 2017;47:29–37.

3 Singh JA, Guyatt G, Ogdie A *et al.* Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Rheumatol 2019;71:5–32.

4 Gladman DD. Psoriatic arthritis. Dermatol Ther 2009;22:40–55.

5 Costa L, Perricone C, Chimenti MS *et al.* Switching between biological treatments in psoriatic arthritis: a review of the evidence. Drugs R D 2017;17:509–22.

6 Ixekizumab [prescribing information]. Indianapolis, IN: Eli Lilly and Company, 2017.

7 Mease PJ, van der Heijde D, Ritchlin CT *et al.* Ixekizumab, an interleukin-17a specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76:79–87.

8 Nash P, Kirkham B, Okada M *et al.* Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-

blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017;389:2317–27.

9 Genovese MC, Combe B, Kremer JM *et al.* Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2. Rheumatology 2018;57: 2001–11.

10 Fagerli KM, Lie E, van der Heijde D *et al.* Switching between TNF inhibitors in psoriatic arthritis: data from the NOR-DMARD study. Ann Rheum Dis 2013;72: 1840–4.

11 Mease PJ, Karki C, Liu M *et al.* Discontinuation and switching patterns of tumour necrosis factor inhibitors (TNFis) in TNFi-naive and TNFi-experienced patients with psoriatic arthritis: an observational study from the US-based Corrona Registry. RMD Open 2019;5: e000880.

12 Saad AA, Ashcroft DM, Watson KD, Hyrich KL *et al.* Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther 2009;11:R52.