Chinese Medical Journal®

Comparative efficacy of secukinumab against adalimumab and infliximab in patients with moderate-to-severe plaque psoriasis

Ran Pan[1], Xiaolun Wang[1], Min Shu[1], Jaydeep Das[2], Manik Kalra[2], Zhidong Wang[1]

[1]Beijing Novartis Pharma Co. Ltd., Shanghai, China;
[2]Novartis Healthcare Pvt. Ltd., Hyderabad, India.

Abstract

Background: Psoriasis is a common, chronic, immune-mediated inflammatory skin disease with increased epidermal proliferation. The objective of this review was to systematically identify the evidence and perform a network meta-analysis (NMA) to estimate the relative efficacy of secukinumab (SEC) against adalimumab (ADA) and infliximab (INF) for the treatment of moderate-to-severe plaque psoriasis.

Methods: A systematic literature review (SLR) was conducted according to a pre-specified protocol to identify relevant studies. Initially, the databases were searched from database inception till June 2013, and the SLR was updated in April 2020. The eligibility criteria included adult patients (≥18 years old) with moderate-to-severe plaque psoriasis, and the SLR included randomized controlled trials (RCTs). The comparators of interest were SEC, ADA, INF, and placebo (PLA), while outcomes of interest were Psoriasis Area and Severity Index (PASI) (50, 75, and 90) at weeks 12, 16, and 24. A Bayesian NMA for PASI was utilized with a framework that evaluated the probability of PASI responses in different categories of PASI thresholds within a single model.

Results: A total of 23 RCTs that assessed the efficacy of SEC, ADA, and INF in patients with moderate-to-severe plaque psoriasis were identified. At 12 weeks, SEC was associated with a significantly better response compared with PLA and ADA for PASI 75 and 90, while response results were comparable against INF. At 12 weeks, risk ratio (95% confidence interval) derived from NMA for SEC *vs*. ADA and INF for PASI 75 was 1.35 (1.19, 1.57) and 1.01 (0.90, 1.18), respectively. At the 16-week and 24-week time interval, SEC was significantly better than PLA, ADA, and INF for PASI 75 and 90.

Conclusion: Efficacy of SEC in the treatment of patient populations with moderate-to-severe plaque psoriasis is well demonstrated through NMA.

Keywords: Moderate-to-severe plaque psoriasis; Secukinumab against adalimumab and infliximab; Indirect comparison; PASI response

Introduction

Psoriasis is a common, chronic, inflammatory, immune-mediated proliferative skin disorder that predominantly involves the skin, nails, and joints.[1] About 90% of psoriasis cases correspond to chronic plaque-type psoriasis (psoriasis vulgaris), which is characterized by well-demarcated, bright red plaques covered by adherent silvery white scales.[2] The plaques can be itchy and sore; the skin may crack and bleed in severe cases. Psoriasis (refers to plaque psoriasis in this article) results in profound functional, psychological, and social morbidity, with consequent reduced levels of employment and income for many patients. These effects are not influenced by severity of disease, with several patients stating that despite minimal involvement, psoriasis has had a major effect on their lives. Factors known to contribute to these effects include skin symptoms (e.g., chronic itch, bleeding, scaling, and nail involvement), psoriatic arthritis, and the effect of living with a highly visible, stigmatizing skin disease.[3] Several studies have also reported that patients with psoriasis, particularly those with severe disease, may be at an increased risk of cardiovascular disease, lymphoma, and non-melanoma skin cancer.

People with psoriasis often experience difficulties such as low self-esteem, and maladaptive coping responses; they also have feelings of shame, stigma, and embarrassment regarding their appearance. As a consequence, psoriasis is associated with having a debilitating effect on quality of life (QoL), resulting in great strain being placed on the mental health of many of those who have the condition. A survey on the burden of psoriasis and patient QoL in China

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001817

Correspondence to: Ran Pan, Beijing Novartis Pharma Co. Ltd., Shanghai, China
E-Mail: ruby.pan@novartis.com

Chinese Medical Journal 2022;135(1)
Received: 08-04-2021; **Online:** 09-12-2021 **Edited by:** Lishao Guo

showed that 46% of severe patients have a suicidal tendency, and 7% of patients have committed suicide.[4]

Treatment of psoriasis includes topical therapies (e.g., topical corticosteroids), phototherapies (e.g., ultraviolet B and psoralen, ultraviolet A), conventional systemic treatments (e.g., methotrexate [MTX], cyclosporin), and biologics. Biologics include secukinumab (SEC), etanercept (ETA), adalimumab (ADA), infliximab (INF), ustekinumab, guselkumab (GUS), ixekizumab, and brodalumab. However, algorithm for biologic therapy is not yet standardized, and data addressing treatment strategies are sparse and often incomplete.

In China, INF, ETA, and ADA are covered under the medical insurance catalog, but these biologics are not able to meet the needs of patients with moderate-to-severe plaque psoriasis to quickly achieve clear skin and there have been events that raise safety concerns associated with these treatment options. Hence, there is a need for a new treatment option for patients.

SEC, a fully human antibody to interleukin-17A (IL-17A), is approved for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy. It is the only fully human anti–IL-17A monoclonal antibody that was unanimously recommended by the 2018 China Psoriasis Guidelines and 2019 Psoriasis Biologics Expert Consensus.[5] A number of international clinical trials[6-8] and clinical trial of the anti-IL-17A in Chinese population showed that SEC is effective and can provide comprehensive improvement of symptoms among patients with moderate-to-severe plaque psoriasis.[9] The efficacy and safety data worldwide for up to 5 years have verified the long-term efficacy and safety of SEC.

Considering the absence of head-to-head trials comparing SEC against ADA and INF, a network meta-analysis (NMA) was needed to achieve this comparison indirectly. Therefore, we updated an existing systematic literature review (SLR) in April 2020 to identify evidence from clinical and safety studies of the following current biological treatments for moderate-to-severe plaque psoriasis: SEC, ADA, and INF. We prepared a summary of the identified clinical studies of biological treatments for moderate-to-severe plaque psoriasis and extracted data on the relevant endpoints of interest. Subsequently, we compared the efficacy of SEC 300 mg against ADA 40 mg, INF 5 mg, SEC 150 mg, and placebo (PLA) via our NMA in the treatment of psoriasis, incorporating efficacy data from phase III trials of SEC.

Methods

Literature search

An SLR was conducted in June 2013, which was updated in April 2020 via a search of the key biomedical databases: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL). MEDLINE® In-Process was also searched to ensure that non-indexed citations were retrieved. Search terms were related to each specific facet of psoriasis, randomized controlled trials (RCTs), and interventions.

Study selection

A protocol was prepared prior to conducting the literature review, defining the inclusion and exclusion criteria [Table 1]. The SLR included phase II or III RCTs that had enrolled adult patients (≥18 years) with moderate-to-severe plaque psoriasis. The trials assessing patients with both psoriasis and psoriatic arthritis were excluded. The interventions of interest were SEC, ADA, INF, and PLA. ETA was not considered for NMA as head-to-head trial comparing the efficacy of SEC *vs*. ETA is available, while ustekinumab, GUS, and ixekizumab were not considered as these are not covered under the medical insurance catalog in China. Brodalumab was not considered for analysis as it was recently approved and literature review was updated before its approval. The analysis included RCTs, while all other study types, including non-randomized clinical studies, were excluded. The outcome of interest was the proportion of patients achieving 50%, 75%, 90%, and 100% improvements in Psoriasis Area and Severity Index (PASI) score (PASI 50, PASI 75, PASI 90, and PASI 100, respectively).

Study selection process

All the records retrieved from the literature search were screened based on the abstract and title supplied with each citation. Each citation was screened by a single reviewer, followed by a quality check. Citations that did not match the eligibility criteria were excluded at this "first level screening"; wherever unclear, citations were included. Thereafter, a set of predefined inclusion criteria [Table 1] were applied to the full-text citations. For each study meeting the eligibility criteria, study design, patient demographics, therapy details and efficacy, and safety outcomes were extracted.

Statistical methodology

Concepts and models for NMA

An NMA consists of statistical methods to combine and analyze data from various studies together to obtain a coherent picture of treatment outcomes and compare various treatment options. In multiple comparisons between treatments, a combination of both direct and indirect evidence on each pairwise comparison between treatments is called mixed treatment comparison (MTC). NMA is a tool for empirical analysis of these data. The analysis to conduct MTC follows several steps, including (i) exploratory analysis, (ii) model specification, and (iii) fitting and selection.

NMA models

The statistical models that were used for evidence synthesis related the underlying outcome to the effect of treatments and any other factors (covariates). The models were adapted from Report of the International Society for

Table 1: Summary protocol of secukinumab against adalimumab and infliximab in patients with moderate-to-severe plaque psoriasis.

Criteria	Inclusion	Exclusion
Population	• Adults (≥18 years old) with moderate-to-severe chronic plaque-type psoriasis • Adults with severe progressive or uncontrolled psoriasis	• Children with psoriasis • Patients with types of psoriasis other than plaque psoriasis (i.e., nail, palmoplantar, pustular, erythrodermic, and guttate psoriasis); if population is mixed, exclude only if plaque psoriasis is not separately analyzed • Patients with mild psoriasis; if population is mixed, exclude only if moderate to severe psoriasis is not separately analyzed
Interventions	• SEC	• Non-biologic treatments for moderate to severe psoriasis as the main treatment of interest • Phototherapy and photochemotherapy as the main treatment of interest • Low-molecular-weight systemics
Comparators	• ADA • INF	
Outcomes	• Efficacy measurements (all reported time points (e.g., 4, 8, 12 weeks) were extracted for each of these outcomes, in addition to the primary endpoint): • PASI 50 (reduction in PASI score of at least 50%) • PASI 75 (reduction in PASI score of at least 75%) • PASI 90 (reduction in PASI score of at least 90%) • PASI 100 (complete remission)	
Study design	RCTs	• Observational studies • Non-randomized, controlled, prospective clinical trials • Long-term follow-up studies (e.g., open-label follow-up studies without a comparator arm) • Prospective observational studies (e.g., phase IV studies)

PASI: Psoriasis Area and Severity Index; RCT: Randomized controlled trial.

Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2,[10] and NICE TSD2.[11]

An ordinal model was used in the base case for analysis. PASI 100 could not be included in the ordinal model because of a high missing value. Therefore, it was separately analyzed using a binomial model. The PASI scores were modeled in two ways for the MTCs: PASI scores modeled as ordinal categories for PASI <50, PASI 50 to 74, PASI 75 to 89, and PASI ≥90 for different weeks; PASI scores analyzed separately for PASI 100 using binomial models for different weeks.

Model parameters were estimated using the Markov Chain Monte Carlo (MCMC) method implemented in OpenBUGS/WinBUGS software packages. All analyses were performed using R version 3.6.1 (http://www.r-project.org/) and Rstudio version 1.1.456. For the ordinal MTCs, the value one was added to PASI 75 (if PASI 90 was not missing) when 0 counts occurred in the network.

Model fitting and selection

The MCMC simulation method was used to generate the posterior distributions of the model parameters (e.g., treatment effects). Generally, 50,000 simulations were run, with a burn-in of 20,000 in order to achieve convergence of the distinct MCMC chains for every parameter. The number of simulations was varied to check for convergence. Model fitting was primarily assessed using total residual deviance and visual inspection of MCMC estimates. Deviance information criterion was used to assess the suitability of alternative model assumptions like fixed and random effects.

Results

Evidence identified

A total of 23 RCTs that assessed the efficacy and safety of SEC, ADA, and INF in patients with moderate-to-severe plaque psoriasis were identified. Table 2 presents the summary of study characteristics and treatment details across the included RCTs. The review identified seven studies for SEC, ten for ADA, and six for INF. One study each assessed SEC, ADA, and INF in Chinese patients. A majority of RCTs were double-blind and were conducted across multiple centers. In terms of study duration, the RCT phase ranged from 12 to 16 weeks, and the open-label phase ranged from 12 to 60 weeks. Generally, baseline characteristics were comparable across the studies, but sample size varied across the trials, ranging from ten patients in Maari *et al*[12] to 814 patients in the

Table 2: Summary of patient characteristics reported across the studies.

Study name	Treatment arm	Randomized	Study characteristics	Age (years), Mean (SD)	Male gender (%)	Mean disease duration (years)	Baseline PASI	
							Mean	SD
Bissonnette *et al*[17]	ADA_80 mg_40 mg	20	SB, NR	56.1 (11.0)	85.0	NR	11.6	5.3
	PLA	10		57.4 (7.6)	60.0	NR	13.1	5.7
Saurat *et al*[18] (CHAMPION trial)	ADA_80 mg_40 mg	108	DB, MI	42.9 (12.6)	64.8	17.9	20.2	7.5
	MTX	110		41.6 (12.0)	66.4	18.9	19.4	7.4
	PLA	53		40.7 (11.4)	66.0	18.8	19.2	6.9
Reich *et al*[15] (EXPRESS trial)	INF_5 mg	298	DB, MI	42.6 (11.7)	69.0	19.1	22.9	9.3
	PLA	76		43.8 (12.6)	79.0	17.3	22.8	8.7
Gordon *et al*[19] (M02–528 trial)	ADA_80 mg_40 mg	46	DB, MI	46 (NR)	71.0	21.0	16.7	NR
ADA_80 mg_80 mg_40 mg	50		44 (NR)	66.0	18.0	14.5	NR	
	PLA	52		43 (NR)	65.0	19.0	16.0	NR
Asahina *et al*[20] (M04–688 trial)	ADA_40 mg	38	DB, SC	47.8 (12.8)	84.2	14.2	25.4	9.0
	ADA_80 mg_40 mg	43		44.2 (14.3)	81.4	14.0	30.2	10.9
	ADA_80 mg	42		43.5 (12.4)	83.3	11.6	28.3	11.0
	PLA	46		43.9 (10.8)	89.1	15.5	29.1	11.8
Barker *et al*[21] (RESTORE-1 trial)	INF_5 mg	653	DB, MI	44.1 (NR)	67.0	18.8	21.4	8.0
	MTX	215		41.9 (NR)	69.0	17.0	21.1	7.6
Menter *et al*[13] (REVEAL trial)	ADA_80 mg_40 mg	814	DB, MI	44.1 (13.2)	67.1	18.1	19.0	7.1
	PLA	398		45.4 (13.4)	64.6	18.4	18.8	7.1
Torii *et al*[22]	INF_5 mg	35	DB, NR	46.9 (13.0)	62.9	14.2	NR	NR
	PLA	19		43.3 (12.3)	73.7	11.1	NR	NR
Menter *et al*[23] (EXPRESS II trial)	INF_3 mg	313	DB, MI	43.4 (12.6)	65.8	18.1	20.1	7.9
	INF_5 mg	314		44.5 (13.0)	65.0	19.1	20.4	7.5
	PLA	208		44.4 (12.5)	69.2	17.8	19.8	7.7
Maari *et al*[12]	ADA_80 mg_40 mg	10	DB, SC	55.7 (11.8)	90.0	NR	11.5	6.3
	PLA	10		49 (10.9)	90.0	NR	10.4	4.5
Gottlieb *et al*[24] (SPIRIT trial)	INF_3 mg	99	DB, SC	NR	70.7	NR	NR	NR
	INF_5 mg	99		NR	73.7	NR	NR	NR
	PLA	51		NR	60.8	NR	NR	NR
Langley *et al*[7] (CAIN457A2302 – Erasure trial)	SEC_150 mg	245	DB, MI	44.9 (13.3)	68.6	17.5	22.3	9.8
	SEC_300 mg	245		44.9 (13.5)	69.0	17.4	22.5	9.2
	PLA	248		45.4 (12.6)	69.4	17.3	21.4	9.1
Langley *et al*[7] (CAIN457A2303 – Fixture trial)	SEC_150 mg	327	DB, MI	44.5	72.2	15.8	23.9	NR
	SEC_300 mg	327		45.4	68.5	17.3	23.7	NR
	ETA	326		43.8	71.2	16.4	23.2	NR
	PLA	326		44.1	72.7	16.6	24.1	NR
Mrowietz[25] (CAIN457A2304 – SCULPTURE trial)	SEC_150 mg	482	DB, MI	45.3	63.3	17.2	24.0	NR
	SEC_300 mg	484		46.7	63.8	17.4	23.3	NR
Blauvelt *et al*[26] (CAIN457A2308 – FEATURE trial)	SEC_150 mg	59	DB, MI	46 (15.1)	67.8	NR	20.5	8.3
	SEC_300 mg	59		45.1 (12.6)	64.4	NR	20.7	8.0
	PLA	59		46.5 (14.1)	66.1	NR	21.1	8.5
Paul *et al*[27] (CAIN457A2309 – JUNCTURE trial)	SEC_150 mg	61	DB, MI	43.9 (14.4)	67.2	20.6	22.0	8.9
	SEC_300 mg	60		46.6 (14.23)	76.7	21.0	18.9	6.4
	PLA	61		43.7 (12.74)	62.3	19.9	19.4	6.7
Blauvelt *et al*[6] (VOYAGE 1 trial)	GUS_100 mg	329		43.9 (12.74)	72.9	17.9	22.1	9.5
	ADA_80 mg_40 mg	334	DB, MI	42.9 (12.58)	74.6	17.0	22.4	9.0
	PLA	174		44.9 (12.9)	68.4	17.6	20.4	8.7
Reich *et al*[28] (VOYAGE 2 trial)	GUS_100 mg	496	DB, MI	43.7 (12.2)	70.4	17.9	21.9	8.8
	ADA_80 mg_40 mg	248		43.2 (11.9)	68.5	17.6	21.7	9.0
	PLA	248		43.3 (12.4)	69.8	17.9	21.5	8.0

(*continued*)

Table 2
(continued).

Study name	Treatment arm	Randomized	Study characteristics	Age (years), Mean (SD)	Male gender (%)	Mean disease duration (years)	Baseline PASI	
							Mean	SD
Gordon *et al*[29] (X-PLORE trial)	GUS_100 mg	208	DB, MI	44.0	72.0	18.5	20.9	8.1
	ADA_80 mg_40 mg	43		50.0	70.0	19.3	20.2	7.6
	PLA	42		46.5	67.0	18	21.8	10.0
Cai *et al*[30]	ADA_80 mg_40 mg	338	DB, SC	43.1 (11.91)	75.1	14.8	28.2	12.0
	PLA	87		43.8 (12.45)	66.7	15.8	25.6	11.0
Zhang *et al*[9]	SEC_300 mg	221	DB, SC	39 (11.6)	80.1	NR	27.3	10.9
	SEC_150 mg	110		40.5 (10.8)	76.4	NR	26.5	10.6
	PLA	110		38.7 (10.3)	80.9	NR	26.2	9.3
von Stebut *et al*[31] (CARIMA trial)	SEC_300 mg	48	DB, SC	44.2 (12.9)	77.1	NR	19.3	7.9
	SEC_150 mg	54		46 (14.4)	57.4	NR	21.7	10.5
	PLA	49		45.25 (12.25)	69.4	NR	18.5	5.2
Yang *et al*[32]	INF_5 mg	84	DB, SC	39.4 (12.3)	71.4	16		
	PLA	45		40.1 (11.1)	77.8	16	NR	NR

ADA_80 mg_40 mg: Adalimumab administered subcutaneously with a loading dose of 80 mg followed by 40 mg; ADA_80 mg_80 mg_40 mg: 80 mg of adalimumab at weeks 0 and 1, followed by 40 mg/week beginning at week 2. ADA: Adalimumab; DB: Double-blind; ETA: Etanercept; GUS: Guselkumab; INF: Infliximab; MI: Multicenter International; MTX: Methotrexate; NR: Not Reported; PASI: Psoriasis Area and Severity Index; PLA: Placebo; SB: Single-blind; SC: Single-center; SD: Standard Deviation; SEC: Secukinumab.

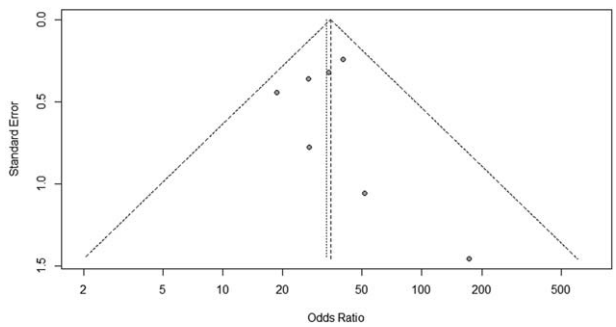

Figure 1: Funnel plot of adalimumab *vs.* placebo.

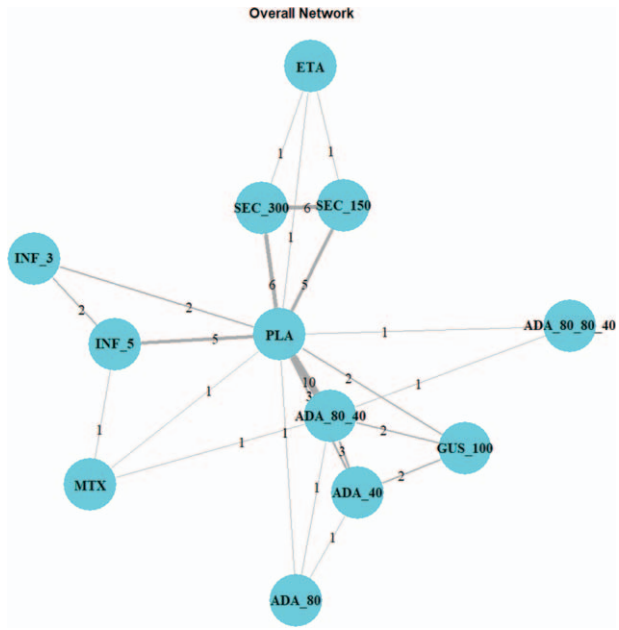

Figure 2: Master network diagram for studies contributing for PASI outcome (base-case analysis). ADA: Adalimumab; ETA: Etanercept; GUS: Guselkumab; INF: Infliximab; MTX: Methotrexate; PASI: Psoriasis Area and Severity Index; PLA: Placebo; SEC: Secukinumab.

REVEAL trial.[13] Mean age, PASI at baseline, and disease duration were found to be comparable across the studies. There is no publication bias present for ADA (40 mg followed by one 80 mg dose) *vs*. PLA. Due to very small number of studies (three studies), publication bias cannot be assessed for INF 5 mg *vs*. PLA. Figure 1 presents the funnel plot for ADA (40 mg followed by one 80 mg dose) *vs*. PLA for PASI75 output at week 12.

Figure 2 presents the master network diagram for studies contributing to the analysis. The numeric value represents the number of studies assessing two different interventions. ETA, GUS, and MTX are presented because they act as a common comparator.

Table 3 presents a summary of risk ratios (RRs) for SEC 300 mg *vs*. comparators for PASI (50, 75, and 90) at different time intervals. At 8 weeks, NMA results showed that SEC 300 mg was associated with a significantly better response compared with ADA for PASI 50, 75, and 90. However, SEC 300 mg was found to be comparable with INF 5 mg for PASI 50, 75, and 90. At 12 weeks, NMA results showed that SEC 300 mg was associated with a significantly better response compared with ADA for PASI 50 (RR: 1.19; 95% confidence interval [CI]: 1.09, 1.31), PASI 75 (RR: 1.39; 95% CI: 1.18, 1.65), and PASI 90 (RR: 1.91; 95% CI: 1.40, 2.62). However, SEC 300 mg was

Table 3: Summary of RRs for SEC 300 mg *vs.* comparators for PASI (50, 75, and 90).

Treatment	PASI 50; mean RR (95% CI)	PASI 75; mean RR (95% CI)	PASI 90; mean RR (95% CI)
8 weeks			
PLA	8.29 (6.76, 10.12)	31.95 (24.12, 42.07)	166.01 (112.60, 241.40)
ADA 40 mg	1.24 (1.13, 1.38)	1.65 (1.34, 2.05)	2.52 (1.71, 3.63)
INF 5 mg	1.03 (0.97, 1.10)	1.08 (0.92, 1.28)	1.18 (0.85, 1.63)
SEC 150 mg	1.08 (1.04, 1.14)	1.23 (1.11, 1.36)	1.49 (1.24, 1.80)
12 weeks			
PLA	8.53 (7.06, 10.56)	21.22 (16.49, 27.87)	97.55 (68.40, 141.30)
ADA 40 mg	1.19 (1.09, 1.31)	1.39 (1.18, 1.65)	1.91 (1.40, 2.62)
INF 5 mg	1.02 (0.95, 1.11)	1.04 (0.90, 1.24)	1.09 (0.79, 1.57)
SEC 150 mg	1.06 (1.02, 1.12)	1.14 (1.05, 1.24)	1.31 (1.11, 1.56)
16 weeks			
PLA	6.75 (5.69, 8.02)	14.99 (12.11, 18.57)	57.49 (42.89, 76.49)
ADA 40 mg	1.20 (1.11, 1.32)	1.42 (1.24, 1.67)	2.01 (1.56, 2.67)
INF 5 mg	1.10 (1.02, 1.21)	1.21 (1.05, 1.44)	1.51 (1.13, 2.08)
SEC 150 mg	1.03 (1.01, 1.07)	1.08 (1.02, 1.15)	1.19 (1.06, 1.35)
24 weeks			
PLA	7.29 (5.92, 8.94)	16.82 (12.79, 21.84)	51.36 (35.24, 72.45)
ADA 40 mg	1.28 (1.01, 1.92)	1.58 (1.03, 2.90)	2.25 (1.06, 5.33)
INF 5 mg	1.19 (1.01, 1.61)	1.41 (1.02, 2.25)	1.86 (1.04, 3.74)
SEC 150 mg	1.05 (1.00, 1.13)	1.10 (1.00, 1.27)	1.22 (1.00, 1.56)

Green color denotes significantly better results in favor of SEC 300 mg. ADA: Adalimumab; CI: Confidence interval; INF: Infliximab; PASI: Psoriasis Area and Severity Index; PLA: Placebo; RR: Risk Ratio; SEC: Secukinumab.

found to be comparable with INF 5 mg for PASI 50 (RR: 1.02; 95% CI: 0.95, 1.11), PASI 75 (RR: 1.04; 95% CI: 0.90, 1.24), and PASI 90 (RR: 1.09; 95% CI: 0.79, 1.57).

Significantly better PASI response was achieved at 16 weeks [Table 3]. At 16 weeks, NMA results showed that SEC 300 mg achieved a significantly better response compared with all four comparators: ADA, INF, SEC 150 mg, and PLA. SEC 300 mg was associated with a significantly better response compared with ADA for PASI 50 (RR: 1.20; 95% CI: 1.11, 1.32), PASI 75 (RR: 1.42; 95% CI: 1.24, 1.67), and PASI 90 (RR: 2.01; 95% CI: 1.56, 2.67). Similarly, SEC 300 mg was associated with a significantly better response than INF 5 mg for PASI 50 (RR: 1.10; 95% CI: 1.02, 1.21), PASI 75 (RR: 1.21; 95% CI: 1.05, 1.44), and PASI 90 (RR: 1.51; 95% CI: 1.13, 2.08). Similar to 16 weeks, at 24 weeks, NMA results showed that SEC 300 mg achieved a significantly better response compared with all four comparators: ADA, INF, SEC 150 mg, and PLA. SEC 300 mg was associated with a significantly better response compared with ADA for PASI 50 (RR: 1.28; 95% CI: 1.01, 1.92), PASI 75 (RR: 1.58; 95% CI: 1.03, 2.09), and PASI 90 (RR: 2.25; 95% CI: 1.06, 5.33). Similarly, SEC 300 mg was associated with a significantly better response than INF 5 mg for PASI 50 (RR: 1.19; 95% CI: 1.01, 1.61), PASI 75 (RR: 1.41; 95% CI: 1.02, 2.25), and PASI 90 (RR: 1.86; 95% CI: 1.04, 3.74). Figure 3 presents the results for PASI 50, 75, and 90 at 12 weeks comparing other treatment options *vs.* SEC 300 mg.

PASI 100 analysis results

PASI 100 outcomes were assessed separately using a Bayesian binomial model with a logit link. Figure 4 presents the network diagram for studies contributing to the analysis for PASI 100 at 12, 16, and 24 weeks. The numeric value represents the number of studies assessing two different interventions. GUS and ETA are presented because they act as a common comparator.

Analysis for PASI 100 was feasible against ADA, PLA, and SEC 150 mg at 12 and 16 weeks [Table 4]. NMA results showed that SEC 300 mg was associated with a better response against ADA at 12 and 16 weeks, but statistical significance was achieved only at 16 weeks (RR: 5.87; 95% CI: 1.88, 13.65). Results against ADA and INF at 24 weeks were not interpretable because of "0" PLA response.

Discussion

We updated an existing SLR in April 2020 to identify the most recent studies with respect to SEC, ADA, and INF. The SLR was updated to conduct an indirect treatment comparison of SEC against ADA, INF, and PLA as the comparators, with the outcomes of interest being PASI 50, 75, and 90 at weeks 12, 16, and 24. Bayesian NMA for PASI was utilized with a framework that evaluated the probability of PASI responses at different categories of PASI thresholds (50, 75, and 90) within a single model. A Bayesian multinomial model with a probit link was used, which assumes an underlying continuous variable that has been categorized by specifying cutoff points. An MCMC simulation method was used to generate the posterior distributions of the model parameters. The random effects model results provide pooled probabilities of achieving PASI 50, 75, and 90 responses for each treatment of interest; RRs of all pairwise treatment PASI 100 outcomes

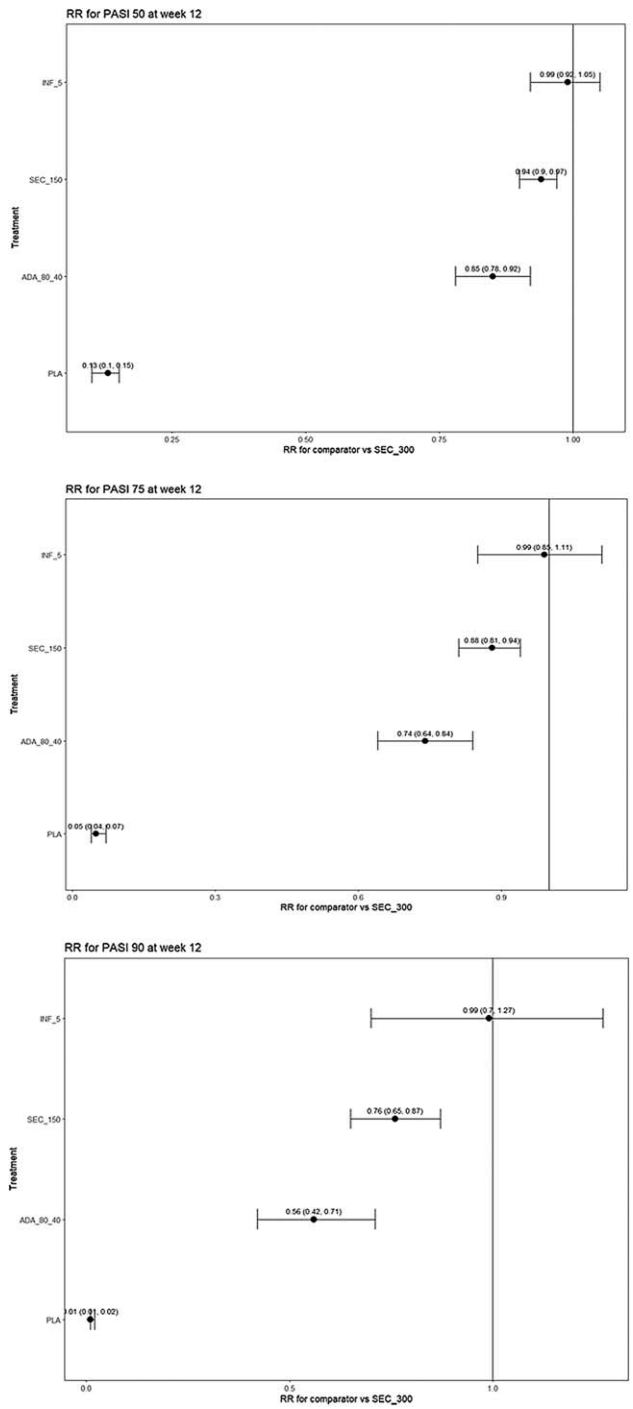

Figure 3: PASI response results for other treatment options *vs.* SEC 300 mg at 12 weeks. PASI: Psoriasis Area and Severity Index; RR: Risk ratio; SEC: Secukinumab.

were assessed separately using a Bayesian binomial model with a logit link. For PASI 100, analysis against ADA was feasible at 12, 16, and 24 weeks, while analysis against INF was feasible at 24 weeks only.

A total of 23 RCTs that assessed the efficacy of SEC, ADA, and INF in patients with moderate-to-severe plaque psoriasis were identified. Of these 23 studies, 16 were included from the original SLR, and 7 were identified from the SLR update. No publication bias was observed for ADA (40 mg followed by one 80 mg dose) *vs*. PLA. The NMA results showed that at 12 weeks, SEC 300 mg was associated with a significantly better response compared with PLA and ADA for PASI (50, 75, and 90) responses, and SEC 300 mg response results were comparable with INF. At 16-week and 24-week time intervals, SEC 300 mg was significantly better than PLA, ADA, and INF for PASI (50, 75, and 90) responses. For PASI 100, SEC 300 mg was associated with a better response compared with ADA at the 12-week and 16-week time intervals, but statistical significance was achieved only at the 16-week interval. The NMA results were consistent with previously conducted analyses by Sawyer *et al*[14], depicting better response with SEC compared to ADA and comparable response *vs*. INF. Trial level data also suggested comparable PASI 75 response rate against PLA with SEC and INF. FIXTURE[7] and ERASURE trial[7] showed 81.6% and 77.1% of SEC 300 mg treated patients achieved PASI 75 response, respectively, and EXPRESS trial demonstrated that 80% of patients treated with INF achieved PASI 75 response.[15] A variation in results was observed across geographies; the trial specifically conducted in Chinese showed higher PASI 75 response with SEC 300 mg compared to PLA (97.7% *vs*. 3.7%) at 12 weeks' time-interval [Supplemenary file, http://links.lww.com/CM9/A796].[16]

The strengths of this SLR involve searching key bibliographic databases and adopting a standard methodology following predefined eligibility criteria established in a protocol. The SLR identified recent data for the interventions of interest.

There were a few limitations associated with the SLR. Only ADA and INF were considered active comparators. Therefore, we could compare RRs for only these treatments. As with all meta-analyses, certain limitations should be considered when interpreting the results. The clinical trials varied in terms of study design and patient populations (i.e., heterogeneity between trials). Where possible, only robust studies of similar design have been included. In some analyses, the number of patients experiencing outcomes was very low, which meant results could be affected by small changes. Where response rates are low, it does mean that one or two patients experiencing one of these events can lead to significant results. Where possible, MTCs have been conducted to meet health technology assessment requirements. Nonetheless, results should be interpreted with caution. This method is consistent with previously conducted NMA.

Response rate at primary endpoint of control arm (e.g., PLA arm) was replicated for the maintenance period (last observation carry forward method) where studies have treatment switch from control arm to treatment arm for non-responders in the control arm after primary endpoint. SEC 300 mg was found to have superior efficacy compared with ADA at 12, 16, and 24 weeks in terms of PASI response (50, 75, and 90). Compared with INF, SEC had significantly better PASI (50, 75, and 90) responses at 16 and 24 weeks, whereas results were comparable at 12 weeks. Efficacy of SEC in the treatment of patient populations with moderate-to-severe plaque psoriasis was demonstrated well through MTCs.

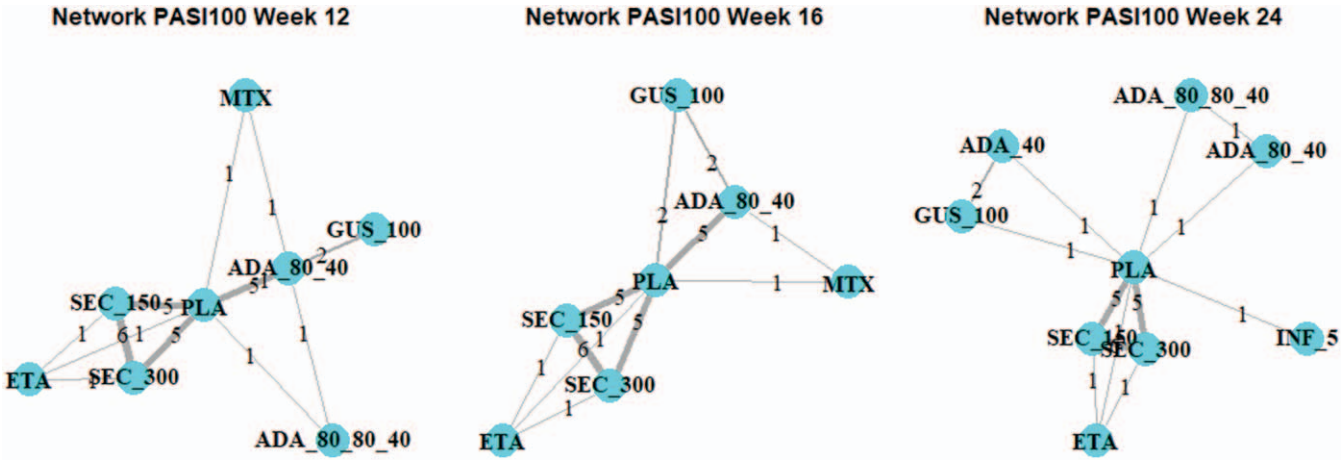

Figure 4: Network diagram for studies contributing for PASI 100 at 12, 16, and 24 weeks. ADA: Adalimumab; ETA: Etanercept; GUS: Guselkumab; INF: Infliximab; MTX: Methotrexate; PASI: Psoriasis Area and Severity Index; PLA: Placebo; SEC: Secukinumab.

Table 4: Summary of RRs for SEC 300 mg *vs.* comparators for PASI 100.

Treatment	12 weeks Mean RR (95% CI)	16 weeks Mean RR (95% CI)	24 weeks Mean RR (95% CI)
PLA	146.95 (43.67, 515.10)	141.65 (55.55, 335.80)	558.81 (124.80, 1927.02)
ADA 40 mg	4.67 (0.96, 14.13)	5.87 (1.88, 13.65)	0.01 (0, 0.06)
SEC 150 mg	1.68 (1.40, 2.03)	1.44 (1.20, 1.83)	1.89 (1.36, 2.70)
INF 5 mg	NA	NA	0.01 (0, 0.07)

Green color denotes significantly better results in favor of SEC 300 mg. ADA: Adalimumab; CI: Confidence interval; INF: Infliximab; NA: Not applicable; PASI: Psoriasis Area and Severity Index; PLA: Placebo; RR: Risk Ratio; SEC: Secukinumab.

References

1. Dogra S, Mahajan R. Psoriasis: epidemiology, clinical features, co-morbidities, and clinical scoring. Indian Dermatol Online J 2016;7:471–480. doi: 10.4103/2229-5178.193906.
2. Rendon A, Schakel K. Psoriasis pathogenesis and treatment. Int J Mol Sci 2019;20:1475. doi: 10.3390/ijms20061475.
3. Samarasekera EJ, Smith CH. National Institute of Health and Care Excellence; Royal College of Physicians. Psoriasis: guidance on assessment and referral. Clin Med (Lond) 2014;14:178–182. doi: 10.7861/clinmedicine.14-2-178.
4. Chen XL, Zheng LY, Zhang H, Zhang JZ, Zhang CL, Ju M, *et al*. Disease burden and quality of life in patients with psoriasis: an internet based questionnaire survey (in Chinese). Chin J Dermatol 2019;52:791–795. doi: 10.35541/cjd.20190247.
5. Committee on Psoriasis, Chinese Society of Dermatology. Guideline for the diagnosis and treatment of psoriasis in China (2018 complete edition) (in Chinese). Chin J Dermatol 2019;52:667–710. doi: 10.35541/cjd.20190847.
6. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, *et al*. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol 2017;76:405–417. doi: 10.1016/j.jaad.2016.11.041.
7. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, *et al*. Secukinumab in plaque psoriasis - results of two phase 3 trials. N Engl J Med 2014;371:326–338. doi: 10.1056/NEJMoa1314258.
8. Thaci D, Blauvelt A, Reich K, Tsai TF, Vanaclocha F, Kingo K, *et al*. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol 2015;73:400–419. doi: 10.1016/j.jaad.2015.05.013.
9. Zhang J, Gu H, Gu J. Efficacy of secukinumab in Chinese moderate to severe psoriasis patients: results from the CAIN457A2318 study. *Eur Acad Dermatol Venereol* 2019: P1600.
10. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, *et al*. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health 2011;14:429–437. doi: 10.1016/j.jval.2011.01.011.
11. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;33:607–617. doi: 10.1177/0272989x12458724.
12. Maari C, Bolduc C, Nigen S, Marchessault P, Bissonnette R. Effect of adalimumab on sleep parameters in patients with psoriasis and obstructive sleep apnea: a randomized controlled trial. J Dermatolog Treat 2014;25:57–60. doi: 10.3109/09546634.2012.713458.
13. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, *et al*. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol 2008;58:106–115. doi: 10.1016/j.jaad.2007.09.010.
14. Sawyer LM, Cornic L, Levin LA, Gibbons C, Moller AH, Jemec GB. Long-term efficacy of novel therapies in moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis of PASI response. J Eur Acad Dermatol Venereol 2019;33:355–366. doi: 10.1111/jdv.15277.
15. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, *et al*. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005;366:1367–1374. doi: 10.1016/s0140-6736(05)67566-6.
16. Cai L, Zhang JZ, Yao X, Gu J, Liu QZ, Zheng M, *et al*. Secukinumab demonstrates high efficacy and a favorable safety profile over 52 weeks in Chinese patients with moderate to severe plaque psoriasis. Chin Med J 2020;133:2665–2673. doi: 10.1097/cm9.0000000000001163.

17. Bissonnette R, Tardif JC, Harel F, Pressacco J, Bolduc C, Guertin MC. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. Circ Cardiovasc Imaging 2013;6:83–90. doi: 10.1161/CIRCIMAGING.112.975730.
18. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, *et al*. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158:558–566. doi: 10.1111/j.1365-2133.2007.08315.x.
19. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, *et al*. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006;55:598–606. doi: 10.1016/j.jaad.2006.05.027.
20. Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab M04-688 Study Group. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study. J Dermatol 2010;37:299–310. doi: 10.1111/j.1346-8138.2009.00748.x.
21. Barker J, Hoffmann M, Wozel G, Ortonne JP, Zheng H, van Hoogstraten H, *et al*. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol 2011;165:1109–1117. doi: 10.1111/j.1365-2133.2011.10615.x.
22. Torii H, Nakagawa H. Japanese Infliximab Study Investigators. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci 2010;59:40–49. doi: 10.1016/j.jdermsci.2010.04.014.
23. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, *et al*. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007;56:31.e1–15. doi: 10.1016/j.jaad.2006.07.017.
24. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, *et al*. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004;51:534–542. doi: 10.1016/j.jaad.2004.02.021.
25. Mrowietz U, Leonardi CL, Girolomoni G, Toth D, Morita A, Balki SA, *et al*. SCULPTURE Study Group. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). J Am Acad Dermatol 2015;73:27–36.e1. doi: 10.1016/j.jaad.2015.04.011.26.
26. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, *et al*. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol 2015;172:484–493. doi: 10.1111/bjd.13348.
27. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, *et al*. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol 2015;29:1082–1090. doi: 10.1111/jdv.12751.
28. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, *et al*. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol 2017;76:418–431. doi: 10.1016/j.jaad.2016.11.042.
29. Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, *et al*. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. N Engl J Med 2015;373:136–144. doi: 10.1056/NEJMoa1501646.
30. Cai L, Gu J, Zheng J, Zheng M, Wang G, Xi LY, *et al*. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. J Eur Acad Dermatol Venereol 2017;31:89–95. doi: 10.1111/jdv.13746.
31. von Stebut E, Reich K, Thaci D, Koenig W, Pinter A, Korber A, *et al*. Impact of secukinumab on endothelial dysfunction and other cardiovascular disease parameters in psoriasis patients over 52 weeks. J Invest Dermatol 2019;139:1054–1062. doi: 10.1016/j.jid.2018.10.042.
32. Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, Xu JH, *et al*. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. Chin Med J 2012;125:1845–1851.

How to cite this article: Pan R, Wang X, Shu M, Das J, Kalra M, Wang Z. Comparative efficacy of secukinumab against adalimumab and infliximab in patients with moderate-to-severe plaque psoriasis. Chin Med J 2022;135:11–19. doi: 10.1097/CM9.0000000000001817