Secukinumab for the treatment of psoriatic arthritis: comparative effectiveness versus infliximab using a Matching-Adjusted Indirect Comparison

V Strand[1], P Mease[2], IB McInnes[3], P Nash[4], H Thom[5], M Hunger[6], K Gandhi[7], J Palmer[7], S Mpofu[8], S Jugl[8]

[1]Stanford University, Palo Alto, CA, USA; [2]Swedish Medical Center and University of Washington, Seattle, WA, USA; [3]University of Glasgow, Glasgow, UK; [4]University of Queensland, Brisbane, QLD, Australia; [5]University of Bristol, Bristol, UK; [6]Mapi Group, Munich, Germany; [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [8]Novartis Pharma AG, Basel, Switzerland

INTRODUCTION

- As yet, no data are available from head-to-head randomized controlled trials (RCTs) between secukinumab (fully human anti-interleukin 17A) and tumor necrosis factor inhibitors (TNFi) in patients with psoriatic arthritis (PsA).
- This analysis used a Matching-Adjusted Indirect Comparison (MAIC) to assess outcomes in patients with PsA following treatment with secukinumab versus the TNFi, infliximab.

Matching-Adjusted Indirect Comparison

- MAIC (**Figure 1**) is a robust method that has been used in analyses of PsA and other conditions.[1,2]
- Health technology assessment agencies have acknowledged MAIC as a valid method.[3,4]
  - The National Institute for Health and Care Excellence (NICE) has recently published guidance on MAIC confirming the method's ability to account for imbalances in covariates between trials.[4]

METHODS

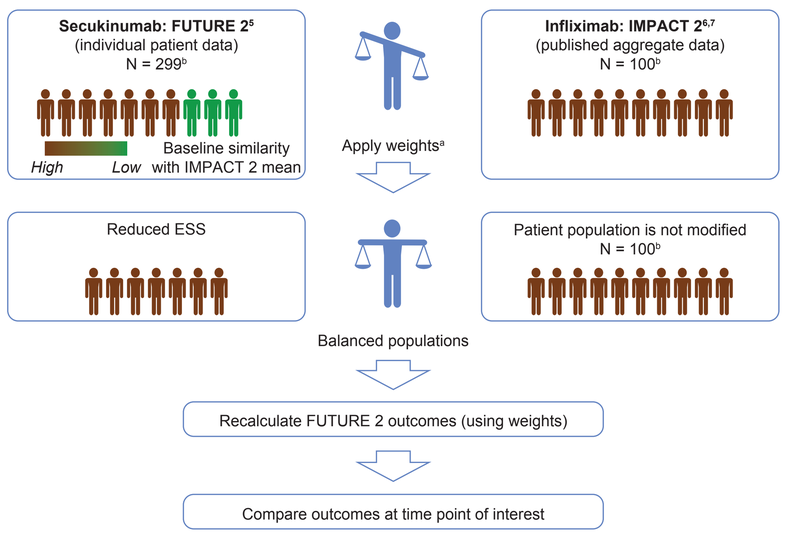
Source data

- The RCTs FUTURE 2[5] and IMPACT 2[6,7] were chosen for this comparison because they were both pivotal trials used to support regulatory approval (**Figure 2**).
  - In IMPACT 2, missing American College of Rheumatology (ACR) data were handled using non-responder imputation (NRI) except at week 54, when missing data were set equal to treatment failure (a form of NRI) and missing values excluded for any other reason.
  - The most appropriate imputation methods to match IMPACT 2 were used.

Methodology

- Individual patient data from the pooled secukinumab arms of FUTURE 2 were weighted to match aggregate patient baseline characteristics of the infliximab arm of IMPACT 2.
  - The placebo arms were also matched.
- Placebo-adjusted comparisons were only possible up to week 16 (**Figure 2**).
- The baseline characteristics matched were identified as effect modifiers or prognostic factors by expert consensus and regression analysis, consistent with recent NICE guidance (**Table 1**).
- Strict thresholds were avoided when interpreting *p* values, as per the American Statistical Association guidance.[8] Instead, values between 0.1 and 0.001 were considered as 'increasing evidence' (weak through moderate to strong) and values below 0.001 as 'strong evidence' of data incompatibility with the null hypothesis (absence of effect).[9]

Figure 1. Matching-Adjusted Indirect Comparison



[a]Weights were derived by logistic regression analyses.
[b]Patient numbers for the active treatment arms in each study are shown; placebo arms were also matched in this analysis (not shown).
ESS, effective sample size.

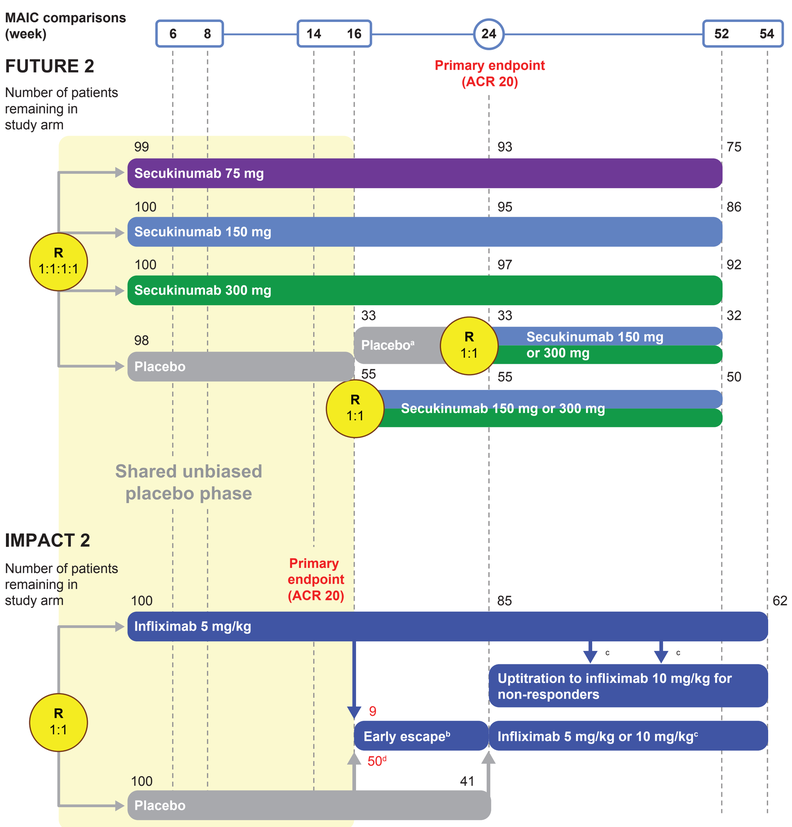
RESULTS

- Before matching, there was heterogeneity in the patient populations between FUTURE 2 and IMPACT 2, and after matching there was near-homogeneity for matched parameters, but with a reduced effective sample size (ESS) for FUTURE 2 (**Table 1**).
- ACR responses are shown in **Figure 3** and changes from baseline in 36-item Short-Form Health Survey (SF-36) scores in **Table 2**.

Placebo arm response after matching

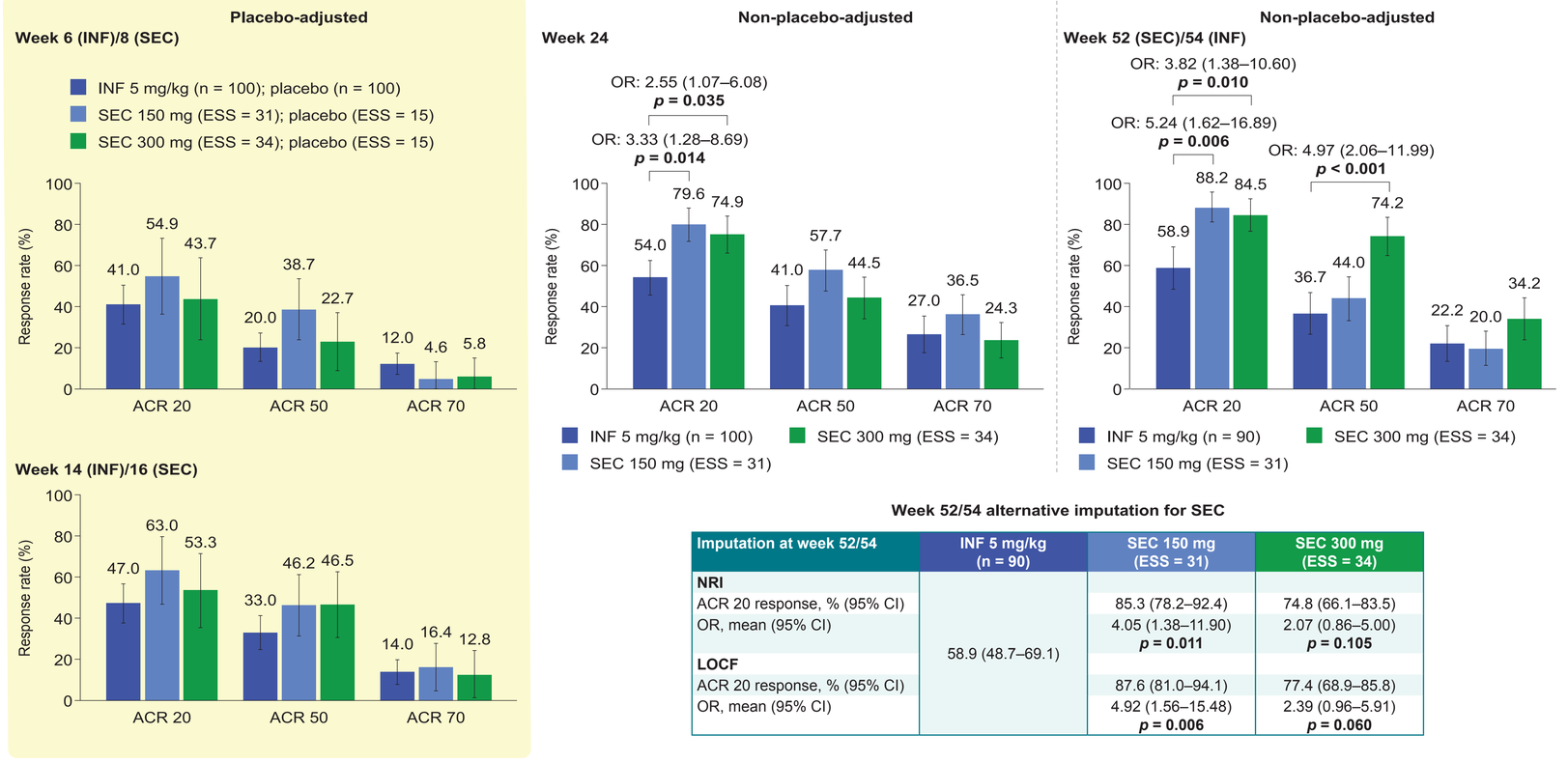
- Week 14/16 **ACR 20** responses were **11.0%** (IMPACT 2) and **8.4%** (FUTURE 2), and **ACR 50** responses were **3.0%** (IMPACT 2) and **2.1%** (FUTURE 2).

Figure 2. Comparison of FUTURE 2 and IMPACT 2 study designs



[a]Patients who had a ≥ 20% improvement from baseline in both SJC and TJC; patients who had a < 20% improvement in both SJC and TJC were re-randomized to secukinumab.
[b]Patients who had a < 10% improvement from baseline in both SJC and TJC.
[c]Patients randomized to infliximab 5 mg/kg who had a < 20% improvement from baseline in the combined SJC and TJC had their infliximab dose increased to 10 mg/kg at weeks 38 and 46.
[d]Includes three patients in the placebo group who received infliximab at week 0 in error.
Placebo-adjusted MAIC comparisons were possible only up to week 16 because of the placebo cross-over design/definition of treatment failure of both trials (the numbers of patients in IMPACT 2 who entered early escape at week 16 are indicated by red numerals).
ACR, American College of Rheumatology; ACR 20, ≥ 20% improvement according to the ACR response criteria; MAIC, Matching-Adjusted Indirect Comparison; R, randomization; SJC, swollen joint count; TJC, total joint count.

Figure 3. Placebo-adjusted and non-placebo-adjusted results for ACR comparisons (biologic-naïve)



Week 52/54 alternative imputation for SEC

Imputation at week 52/54	INF 5 mg/kg (n = 90)	SEC 150 mg (ESS = 31)	SEC 300 mg (ESS = 34)
NRI	58.9 (48.7–69.1)		
ACR 20 response, % (95% CI)		85.3 (78.2–92.4)	74.8 (66.1–83.5)
OR, mean (95% CI)		4.05 (1.38–11.90) ***p* = 0.011**	2.07 (0.86–5.00) ***p* = 0.105**
LOCF			
ACR 20 response, % (95% CI)		87.6 (81.0–94.1)	77.4 (68.9–85.8)
OR, mean (95% CI)		4.92 (1.56–15.48) ***p* = 0.006**	2.39 (0.96–5.91) ***p* = 0.060**

All *p* values are based on pairwise comparisons using ORs. ACR 20/50/70 responses are the absolute mean response rate (IMPACT 2) and the predicted mean response rate (FUTURE 2). An OR < 1 favors infliximab; OR > 1 favors secukinumab.
ACR plots: Error bars show 95% CIs. Comparisons in which SEC had statistically significant higher responses than INF are indicated with OR (95% CI) and *p* value. Week 52 FUTURE 2 secukinumab ITT population (observed) was compared with week 54 IMPACT 2 infliximab (MEF/MEX).
Inset table: Week 52 secukinumab ACR 20 responses calculated using NRI and LOCF and compared with published infliximab (MEF/MEX).
ACR, American College of Rheumatology; ACR 20/50/70, ≥ 20/50/70% improvement according to the ACR response criteria; CI, confidence interval; ESS, effective sample size; INF, infliximab; ITT, intention-to-treat; LOCF, last observation carried forward; MEF, missing equals failure; MEX, missing values excluded; NRI, non-responder imputation; OR, odds ratio, SEC, secukinumab.

Table 1. Patient baseline characteristics in IMPACT 2 and FUTURE 2 before and after matching

	Before matching				After matching		
	IMPACT 2	FUTURE 2			FUTURE 2		
	INF 5 mg/kg (n = 100)	SEC 150 mg (n = 100)	SEC 300 mg (n = 100)	Pooled SEC[a] (n = 299)	SEC 150 mg (ESS = 31)	SEC 300 mg (ESS = 34)	Pooled SEC[b] (ESS = 102)
Demographics							
Age, years, mean (SD)	47.1 (12.8)	46.5 (11.7)	46.9 (12.6)	47.3 (11.9)	47.1 (8.3)	47.4 (8.3)	47.1 (7.7)
Weight, kg, mean (SD)	87.9 (16.5)	91.2 (19.8)	85.4 (18.4)	87.4 (19.7)	90.7 (13.1)	84.3 (9.9)	87.9 (11.7)
Female, n (%)	29 (29.0)	45 (45.0)	49 (49.0)	146 (48.8)	(19.6)[d]	(31.8)[d]	(29.0)[d]
White, n (%)	95 (95.0)	90 (90.0)	96 (96.0)	276 (92.3)	(93.6)[d]	(97.6)[d]	(95.0)[d]
Disease characteristics							
Psoriasis ≥ 3% BSA, n (%)	83 (83.0)	58 (58.0)	41 (41.0)	149 (49.8)	(89.6)[d]	(77.2)[d]	(83.0)[d]
PASI score,[c] mean (SD)	11.4 (12.7)	16.2 (14.3)	11.9 (8.4)	13.6 (11.6)	12.6 (9.7)	9.9 (6.4)	11.4 (8.0)
HAQ-DI score, mean (SD)	1.1 (0.6)	1.2 (0.6)	1.3 (0.6)	1.2 (0.6)	1.1 (0.4)	1.2 (0.4)	1.1 (0.4)
Presence of dactylitis, n (%)	40 (40.0)	32 (32.0)	46 (46.0)	111 (37.1)	(34.5)[d]	(44.7)[d]	(40.0)[d]
Presence of enthesitis, n (%)	42 (42.0)	64 (64.0)	56 (56.0)	188 (62.9)	(36.2)[d]	(36.2)[d]	(42.0)[d]
Previous therapy							
Methotrexate use, n (%)	47 (47.0)	46 (46.0)	45 (45.0)	138 (46.2)	(47.3)[d]	(46.1)[d]	(47.0)[d]
TNFi-naive, n (%)	100 (100.0)	63 (63.0)	67 (67.0)	195 (65.2)	(100.0)[d]	(100.0)[d]	(100.0)[d]

[a]Pooled SEC 75 mg (n = 99), 150 mg (n = 100) and 300 mg (n = 100) matched to INF 5 mg/kg arm of IMPACT 2.
[b]Pooled SEC 75 mg, 150 mg and 300 mg data.
[c]PASI data collected only for patients with psoriasis affecting ≥ 3% of their BSA.
[d]Integer population (n) values not available owing to calculation of pooled SEC ESS using the equation: $\frac{(\sum_{i=1}^{n} \omega_i)^2}{\sum_{i=1}^{n} \omega_i^2}$
BSA, body surface area; ESS, effective sample size; HAQ-DI, Health Assessment Questionnaire-Disability Index; INF, infliximab; PASI; Psoriasis Area Severity Index; SD, standard deviation; SEC, secukinumab; TNFi, tumor necrosis factor inhibitor.

Placebo-adjusted comparisons

Week 6/8

- No evidence that ACR responses differed between secukinumab and infliximab.

Week 14/16

- No evidence that ACR or Psoriasis Area Severity Index (PASI) responses differed between secukinumab and infliximab. There was also:
  - greater change from baseline in SF-36 Mental Component Summary (MCS) scores with secukinumab 150 mg than infliximab ($p = 0.008$).

Non-placebo-adjusted comparisons

Week 24

- Moderate evidence that ACR 20 responses were higher with secukinumab 150 mg or 300 mg than infliximab ($p = 0.014$ and $p = 0.035$, respectively). There were also:
  - higher PASI 90 responses with secukinumab 300 mg than infliximab ($p = 0.078$)
  - greater changes from baseline in SF-36 MCS scores with secukinumab 150 mg than infliximab ($p < 0.001$).

Week 52/54

- Moderate evidence that ACR 20 responses were higher with secukinumab 150 mg and 300 mg than infliximab ($p = 0.006$ and $p = 0.010$, respectively).
- Strong evidence that ACR 50 responses were higher with secukinumab 300 mg than infliximab ($p < 0.001$). There were also:
  - higher PASI 75 and PASI 90 responses with secukinumab 300 mg than infliximab ($p = 0.004$ and $p = 0.023$, respectively)
  - greater changes from baseline in SF-36 MCS scores with secukinumab 150 mg than infliximab ($p = 0.003$).
- When the same data were analyzed using NRI or last observation carried forward, similar observations were evident (see inset table in **Figure 3**).

Sensitivity analyses

- Sensitivity analyses were consistent with the main analysis; these analyses:
  - included PsA disease duration, swollen joint counts and C-reactive protein levels
    - week 6/8 and week 14/16 comparisons were not available because the matching algorithm in the placebo arms failed to converge
  - were matched for SF-36 summary scores at baseline (secukinumab 150 mg ESS = 23).

Table 2. Comparison of changes in SF-36 scores

Outcomes	INF 5 mg/kg (n = 100)	SEC 150 mg (ESS = 31)	SEC 300 mg (ESS = 34)
Placebo-adjusted change from baseline (95% CI)			
Week 14/16			
SF-36 PCS	8.0 (5.5–10.5)	7.3 (5.4–9.2)	5.5 (3.4–7.6)
SF-36 MCS	5.0 (2.2–7.8)	**10.4 (7.6–13.3) *p* = 0.008**	4.7 (2.1–7.4)
Non-placebo-adjusted change from baseline (95% CI)			
Week 24			
SF-36 PCS	7.7 (5.8–9.6)	7.8 (6.6–9.1)	7.2 (5.8–8.6)
SF-36 MCS	3.9 (1.6–6.2)	**10.2 (7.9–12.5) *p* < 0.001**	3.7 (1.9–5.6)
Week 52/54			
SF-36 PCS	8.8 (6.5–11.1)	8.3 (6.8–9.8)	8.2 (6.7–9.7)
SF-36 MCS	3.7 (1.7–5.7)	**7.7 (6.0–9.4) *p* = 0.003**	5.3 (3.3–7.2)

LOCF imputation used at all time points.
CI, confidence interval; ESS, effective sample size; INF, infliximab; LOCF, last observation carried forward; MCS, Mental Component Summary; PCS, Physical Component Summary; SEC, secukinumab; SF-36, 36-item Short-Form Health Survey.

Limitations of this Matching-Adjusted Indirect Comparison

- Placebo adjustment was feasible only until week 16 owing to differences in study designs.
- Week 24 was the only common time point at which outcomes were reported in both RCTs.
- Matching led to a small ESS for FUTURE 2 (secukinumab 150 mg ESS = 31, secukinumab 300 mg ESS = 34).
- Limited outcomes data were available for PASI scores (collected only for the subgroup of patients with psoriasis; secukinumab 150 mg ESS = 25, secukinumab 300 mg ESS = 22).

CONCLUSIONS

Placebo-adjusted data

- ACR responses were similar at weeks 6/8 and 14/16 in patients with PsA receiving either secukinumab or infliximab.

Non-placebo-adjusted data

- At weeks 24 and 52/54, secukinumab showed evidence of superiority for symptomatic improvement over infliximab for active PsA at weeks 24 (ACR 20 responses) and 52/54 (ACR 20 and ACR 50 responses).

REFERENCES

1. Kirson NY *et al. J Med Econ* 2013;16:479–89.
2. Signorovitch JE *et al. Pharmacoeconomics* 2010;28:935–45.
3. Thom H *et al. PRM167 Value Health* 2016;19:A100–1.
4. Phillippo DM *et al.* NICE DSU Technical Support Document 18 2016. Available from http://www.nicedsu.org.uk (Accessed March 2017).
5. McInnes IB *et al. Lancet* 2015;386:1137–46.
6. Antoni C *et al. Ann Rheum Dis* 2005;64:1150–7.
7. Kavanaugh A *et al. Ann Rheum Dis* 2007;66:498–505.
8. Wasserstein RL *et al. Am Stat* 2016;70:129–33.
9. Sterne JA *et al. BMJ* 2001;322:226–31.

DISCLOSURES

V Strand has received consultancy fees from AbbVie, Amgen, AstraZeneca, Biogen Idec, Boehringer Ingelheim, Celltrion, Crescendo, Genentech/Roche, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sanofi and UCB. **P Mease** has received research grants from AbbVie, Amgen, Bristol-Myers Squibb, Lily, Novartis, Pfizer and UCB. He has also received consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Corrona, Lily, Merck, Novartis, Pfizer, Sun and UCB, and has been a speaker for AbbVie, Amgen, Celgene, Genentech, Novartis, Pfizer and UCB. **IB McInnes** has received research grants from AstraZeneca, Bristol-Myers Squibb, Celgene and Pfizer. He has also received consulting fees from AbbVie, Bristol-Myers Squibb, Janssen, Merck Sharp & Dohme, Novartis, Pfizer and UCB. **P Nash** has received funding from Novartis Pharma AG for research, consultancy and as a speaker. **H Thom** has received consultancy fees from F. Hoffmann-La Roche AG and Novartis Pharma AG. **M Hunger** is a paid employee of the Mapi Group. The Mapi Group received funding from Novartis Pharma AG for this study. **K Gandhi** and **J Palmer** are paid employees of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. **S Mpofu** and **S Jugl** are paid employees of Novartis Pharma AG, Basel, Switzerland.

ACKNOWLEDGMENTS

Editorial support was provided by Oxford PharmaGenesis, Oxford, UK, which received funding from Novartis Pharma AG, Basel, Switzerland. Mapi Group, Munich, Germany performed the MAIC and associated report.

The study was sponsored by Novartis Pharma AG, Basel, Switzerland.

Poster presented at the Academy of Managed Care and Pharmacy (AMCP) and Speciality Pharmacy Annual Meeting, 27–30 March 2017, Denver, CO, USA.