RANDOMIZED TRIAL REPLICATION USING OBSERVATIONAL DATA FOR COMPARATIVE EFFECTIVENESS OF SECUKINUMAB AND USTEKINUMAB IN PSORIASIS

A Prospective Cohort Study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)

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BACKGROUND

1 Comparative effectiveness studies using observational data can provide evidence to inform clinical evidence where RCTs have not been performed. Such data may also help quantify the efficacy-effectiveness gap between trials and real-world data. They can be affected by biases such as selection or immortal time bias.

2 Characterising ***a target trial***, the ideal trial that would have been done had it been feasible, can provide a structured approach to guide analysis and minimise bias. This includes outlining key aspects of the study such as the eligibility criteria; treatment strategies; assignment procedure; follow-up period; and the causal contrasts of interest; then followed by an application of this design to the observational dataset.

AIM

To perform a benchmarking study to compare the effectiveness of secukinumab (Cosentyx) against ustekinumab (Stelara) using data from BADBIR, and benchmark this estimate against the RCT CLEAR.

RESULTS

Data source		CLEAR	BADBIR				
Missing outcome analysis method		Non-responder imputation, PASI 90 outcome	Complete case analysis (n=265 PS matched; n=549 PS weighted)	Non-responder imputation	Last observation carried forward (n=559 PS matched; n=1106 PS weighted)	Inverse probability of censoring weighting	Multiple imputation
Propensity score weighted analysis (n=1231, ustekinumab 917, secukinumab 314)	Estimated proportion on secukinumab achieving PASI ≤ 2	74.9%	57.4% (48.3-66.4)	23.4% (18.5-28.2)	67.7% (62.0-73.4)	58.2% (48.5-67.9)	57.8% (48.5-67.1)
	Estimated proportion on ustekinumab achieving PASI ≤ 2	60.6%	45.5% (40.4-50.6)	20.4% (17.6-23.2)	58.6% (55.0-62.2)	45.9% (40.7-51.1)	44.7% (39.5-49.9)
	RR	1.24 (1.11-1.37)	1.28 (1.06-1.55)	1.16 (0.91-1.48)	1.16 (1.04-1.29)	1.29 (1.06-1.58)	1.30 (1.04-1.62)
	Standardised difference between study and RCT for RR*	/	0.012	-0.016	-0.030	0.013	0.013
	RD	14.3% (7.2-21.1)	11.9% (1.6-22.1)	2.9% (-2.6-8.5)	9.1% (2.4-15.8)	12.3% (1.4-23.2)	13.1% (1.3-24.9)
	Standardised difference between study and RCT for RD*	/	-0.012	-0.081	-0.034	-0.010	-0.006
Regulatory agreement		/	Y	N	Y	Y	Y
Estimate agreement		/	Y	RR - Y	Y	Y	Y

Table 1: Outcome of absolute PASI ≤ 2 at 12 months for secukinumab compared with ustekinumab (95% confidence intervals in brackets).
PS – propensity score; *Risk ratio and risk difference calculated using MedCalc.net; numbers taken from the CLEAR study PASI 90 non-responder imputation outcome at week 52. Results using PASI 90 as the alternative outcome resulted in similar findings. ^Regulatory agreement – study replicates direction and statistical significance of the RCT finding; Estimate agreement – study treatment effect lies within the 95% CI for treatment effect estimate from the trial; standardised differences calculated as per methods from Franklin *et al*[2].

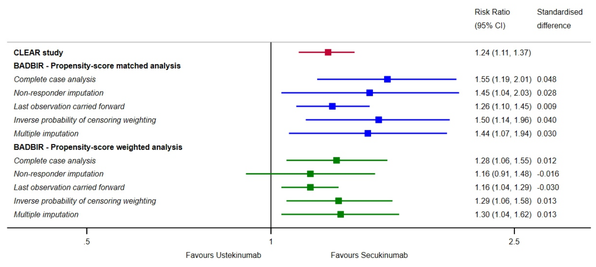

Figure 1: Forest plot summarising the risk ratio estimates for the proportion of participants achieving PASI ≤2 at 12 months comparing secukinumab against ustekinumab using the two propensity score methods and the missing outcome analysis methods.

METHODS

BADBIR - prospective safety registry of patients with psoriasis on systemic therapies established in 2007 in the UK and the Republic of Ireland[1]. Data cutoff August 2019.

Eligible criteria:
1. Patients with chronic plaque psoriasis aged ≥18
2. Allowed any past systemic therapy apart from biologic therapies targeting interleukin(IL)-17 or 23 pathways
3. At least 1 record of PASI ≥12 prior to initiation of biologic
4. Drug initiation on/after September 2013; before September 2018

Treatment strategies:
1. Commencing either ustekinumab or secukinumab
2. Any concomitant topical or systemic therapies allowed; systemic therapies adjusted for
3. Dosing strategies up to individual clinicians
4. Follow-up from initiation of treatment to the earliest of death; loss to follow-up; discontinuation of therapy, or 1 year of follow-up.

Outcome:
1. Proportion reaching PASI ≤2 after 12 months of therapy
2. Proportion reaching 90% in PASI (PASI 90) after 12 months of therapy

DISCUSSION

1 Taking the point estimate from CCA under PS weighting, we see a 17.5% reduction in secukinumab and 15.1% reduction for ustekinumab between efficacy, the effect of a treatment under ideal conditions, and effectiveness, the effect of a treatment under real-world conditions. When counselling patients for the likely outcome of biologic therapies based on figures from clinical trials, clinicians should caveat that the real-world effect is likely 15% lower than that found in clinical trials.

2 A target trial using data from BADBIR was able to replicate the findings from CLEAR to regulatory and estimate agreement using most analytical methods. We found that weighting by PS obtained stable relative effect estimates. We found that NRI was overly conservative and introduced non-differential mis-classification that bias the effect estimate towards the null. We found that CCA, MI and IPCW resulted in similar effect estimates and width of confidence intervals using PS weighting.

3 Clinicians can interpret comparative effectiveness studies using a target trial framework with confidence and utilise this information as an adjunct for shared decision making along with data from RCTs.

Benchmarking trial:
CLEAR[1] - phase IIIB RCT comparing secukinumab (n=337) against ustekinumab (n=339) lasting 52 weeks, Secondary endpoint PASI 90 at week 52 used for benchmarking.

Agreement metrics[2]:
1. *Regulatory agreement* - ability of the study to replicate direction and statistical significance of RCT
2. *Estimate agreement* - study effect estimate lies within 95% confidence interval (CI) of RCT estimate
3. *Standardised difference* between study and RCT

Statistical analysis:
- Propensity score (PS) fitted using multivariable logistic regression, utilised with two methods:
1. Nearest neighbour optimal 1:1 matching, caliper 0.05 (***PS-matched analysis***)
2. Inverse probability treatment weighting (***PS-weighted analysis***)
-Generalised linear models fitted with log link for relative risk ratios; identity link for risk differences

Missing outcome estimation methods:
1. Complete case analysis (CCA)
2. Non responder imputation (NRI)
3. Last observation carried forward (LOCF)
4. Multiple imputation (MI) - 20 datasets
5. Inverse probability of censoring weighting (IPCW)

Strengths and weaknesses of the study

- ✓ Little potential misclassification for diagnosis of psoriasis
- ✓ Availability of PASI data that is not captured in claims databases
- ✘ 45% missing outcome data
- ✘ Bias through knowledge of CLEAR outcome prior to analysis

SUMMARY

Treatment with secukinumab results in a higher proportion of patients reaching a Psoriasis Area and Severity Index (PASI) ≤2 after 12 months of therapy as compared to ustekinumab in BADBIR. There is an efficacy-effectiveness gap for both treatments.

A target trial emulation approach can be used to perform comparative effectiveness studies to both regulatory and estimate agreement with a benchmarking randomized controlled trial (RCT) using data from BADBIR.

1 Blauvelt A et al. (2017) *J Am Acad Dermatol* 76:60-69 2 Franklin JM *et al.* (2019) *Clin Pharmacol Ther* 105:867-877