A Propensity-Score Weighting Approach to Compare Registry and Trial Populations of Patients with Psoriasis on Biologic Therapies

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CONCLUSIONS

The background characteristics between two representative trial and registry populations of patients with psoriasis on biologic therapies are different.

There is a suggestion that a sample representative of the background characteristics of a real-world population of patients with psoriasis had a higher incidence rate of SAEs compared with a sample representative of a psoriasis trial population, but no significant efficacy-effectiveness gap was present between these two sample populations.

These results help further our understanding of the true differences between trial and real-world populations in patients with psoriasis.

BACKGROUND

1 Randomized controlled trials (RCTs) have high internal validity but lower external validity. They are powered for clinically meaningful differences in efficacy outcomes, not rarer safety outcomes.

2 Patients ineligible for RCTs in psoriasis registries have a higher risk of serious adverse events[1,2]. Estimation of this risk difference is limited by accessibility of phase III protocols for exhaustive list of exclusion/inclusion criteria[3].

3 Differences in the distribution of baseline characteristics may may also lead to risk differences between the trial population and trial-eligible patients in the registry population.

AIM

To investigate whether there are any differences in the risk of serious adverse events before and after weighting a registry sample to a trial sample of patients with psoriasis on biologic therapies

METHODS

Registry sample

British Association of Dermatologists Biologic Interventions Register (BADBIR) - prospective safety registry of patients with psoriasis on systemic therapies established in 2007 in the UK and the Republic of Ireland[3].

Inclusion criteria: patients with chronic plaque psoriasis, with follow-up data for 1 year or had a serious infection within 1 year, data lock December 2016. Patients starting etanercept, adalimumab, ustekinumab

Trial sample

PHOENIX I (NCT00267969) and **PHOENIX II** (NCT00307437) phase III multi-centre, multi-national RCTs for ustekinumab in the treatment of psoriasis

Standardisation by Propensity Score

- Estimates the probability to be enrolled in the trial as a function of measured common baseline covariates
- Re-weighting registry participants to be representative of trial sample, and compare differences before and after weighting to infer differences in benefit and risk

Effectiveness outcome: absolute Psoriasis Area and Severity Index (PASI) at 6 months after biologic initiation.

Safety outcome: serious adverse events (SAEs) in first 12 months after biologic initiation.

Analytical steps:

1. Identify common baseline covariates and combine two datasets.
2. Account for missing data using multiple imputation (20 imputed datasets).
3. Identify predictors of trial status.
4. Calculate propensity scores from multivariable logistic regression, estimating probability of each patient for being a trial participant.
5. Use standardised mortality ratio (SMR) weights to re-weigh registry sample population to a "pseudo-trial" sample
6. Compare absolute risk differences in serious adverse events (SAEs) in first 12 months after biologic initiation before and after weighting; obtain 95% confidence intervals using bootstrapping (1000 replications).

Sensitivity analyses

1. Restrict to participants with PASI ≥ 12
2. Restrict to participants who have not had concomitant therapy
3. Restrict to ustekinumab cohort

RESULTS

Registry sample population N=6790; Etanercept 1417, Adalimumab 1549, Ustekinumab 1549
Trial sample population N=2021

Common baseline covariates to trial and registry:
age (5 year categories), gender, body mass index, PASI, alcohol (units/wk), smoking status, comorbidities (asthma, hypertension, angina, previous myocardial infarction, stroke, diabetes, depression, psoriatic arthritis (PsA), ethnicity, previous therapies

Covariate	Trial	Registry
Alcohol (units/wk), mean (SD)	3.4 (5.8)	8.4 (14.0)
Depression	14.8%	22.7%
Female gender	31.2%	40.8%
No. previous non-biologics, mean(SD)	0.9 (1.0)	1.6 (1.0)
No. previous biologics, mean (SD)	0.6 (0.8)	0.3 (0.6)

Table 1: A table illustrating some notable differences between the registry and trial populations.

Multivariable logistic regression (C-statistic 0.82)

Significant predictors for trial status:

Age		**Smoking**	
30-34	OR 0.67 (0.52, 0.87)	< 10 CPD	OR 1.41 (1.15, 1.73)
55-59	OR 1.29 (1.02, 1.62)	10-20 CPD	OR 0.79 (0.65, 0.95)
60-64	OR 1.41 (1.09, 1.84)	> 20 CPD	OR 1.74 (1.42, 2.12)
Ethnicity		**Female gender**	OR 0.53 (0.47, 0.60)
Black	OR 2.11 (1.26, 3.54)	**Alcohol**	OR 0.92 (0.91, 0.92)
Asian	OR 0.53 (0.40, 0.71)	**Depression**	OR 0.59 (0.51, 0.69)
Other	OR 0.54 (0.37, 0.79)	**Angina**	OR 0.19 (0.10, 0.36)
		Asthma	OR 0.71 (0.58, 0.88)
		No. prev systemics	OR 0.42 (0.40, 0.45)
		No. prev biologics	OR 2.31 (2.13, 2.50)

	Absolute PASI < 1.5 at 6 months (%, 95% CI)	Incidence rate of SAE / 1000 person-years (95% CI)
Model 1 - Full registry cohort		
Before weighting	38.0 (36.6, 39.5)	75.0 (68.1, 82.7)
After weighting	37.1 (33.6, 40.6)	65.8 (51.6, 83.7)
Risk difference	1.0 (-2.0, 4.2)	9.3 (-3.9, 22.5)
Model 2 - Population with starting PASI ≥ 12		
Before weighting	37.3 (35.4, 39.3)	79.8 (70.6, 90.1)
After weighting	38.6 (33.1, 44.2)	54.3 (42.8, 69.0)
Risk difference	-1.3 (-6.4, 3.8)	25.4 (14.0, 37.0)
Model 3 - Population without any concomitant therapy		
Before weighting	39.9 (38.2, 41.6)	73.5 (66.0, 81.9)
After weighting	38.5 (33.8, 43.2)	62.2 (48.3, 79.9)
Risk difference	1.3 (-3.2, 5.7)	11.4 (-1.4, 24.6)
Model 4 - Ustekinumab cohort		
Before weighting	41.1 (38.0, 44.3)	89.8 (74.8, 107.8)
After weighting	41.0 (34.3, 47.8)	64.3 (45.3, 91.3)
Risk difference	2.8 (-5.2, 10.8)	25.5 (-1.5, 44.9)

Table 2: The results in the effectiveness and safety outcomes before and after weighting, and the calculated risk differences for the primary model and the sensitivity analyses.

DISCUSSION

1 We show that participants from a large RCT for a biologic therapy for psoriasis were not representative of a real-world UK and Republic of Ireland cohort of patients with psoriasis. There were systematic differences between the two populations, including demographic, lifestyle and disease factors.

2 Our results are congruent with published literature, which show that psoriasis patients in registries who would not have been eligible for enrollment into clinical trials for biologics have a higher risk of SAEs[1,2].

3 We did not find an efficacy-effectiveness gap between the registry and "pseudo-trial" population. Other factors, such as treatment adherence or observation bias, may therefore be more influential in the efficacy-effectiveness gap seen in biologic therapies for psoriasis than the background characteristics of an individual.

Strengths and weaknesses of the study

✓ Compares distribution of real-world to individual participant trial data
✓ Detailed data capture to enable usage of common covariates
✗ Likely unmeasured confounding
✗ Findings may partly be due to genuine differences between countries

ACKNOWLEDGEMENTS

Participants of BADBIR, principal investigators, research nurses, recruiting doctors, BADBIR office team, BADBIR biologics manager, BADBIR steering and data monitoring committees, BADBIR data analysis working group. ZZNY is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship (Ref no: DRF-2015-08-089). This is a summary of independent research funded by the NIHR Doctoral Research Fellowship. The views expressed are those of the author and not necessarily those of the NHS, the NIHR, or the Department of Health. This study, carried out under YODA Project #2017-1706, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C. The interpretation and reporting of research using this data are solely the responsibility of the authors and does not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C.

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