EXAMINING THE RISK OF SERIOUS INFECTION IN PATIENTS WITH PSORIASIS ON BIOLOGIC THERAPIES

A Prospective Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

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SUMMARY

Etanercept, adalimumab and ustekinumab are not associated with a higher risk of serious infections when compared to non-biologic systemic therapies in patients with psoriasis.

The risk of serious infection should not be a discriminator when choosing between these three biologic therapies.

Healthcare professionals should be equally vigilant for serious infections when looking after patients with psoriasis on systemic non-biologic or biologic therapies.

BACKGROUND

1. Adverse events (AE) can lead to discontinuation of biologics for the treatment of psoriasis[1]. Of these AEs, infection is the most common.
2. Serious infections lead to significant morbidity and mortality.
3. Randomised clinical trials are not powered to investigate AEs and have low external validity[2-3].
4. Risk of serious infection in patients with psoriasis on biologics is currently not well-understood.

AIM

To determine whether etanercept, adalimumab and ustekinumab are associated with a higher risk of serious infection as compared to non-biologic systemic therapies for psoriasis

METHODS

British Association of Dermatologists Biologic Interventions Register (BADBIR) - prospective safety registry of patients with psoriasis established in 2007 in the UK and the Republic of Ireland[4].

BIOLOGICS
Etanercept
Adalimumab
Ustekinumab

VS

NON-BIOLOGICS
Methotrexate
Acitretin
Ciclosporin
Fumaric acid esters
Psoralen-UVA
Hydroxycarbamide

Compares a cohort on biologic therapies with a cohort on non-biologic systemic therapies with the same disease severity entry criteria: **Psoriasis Area and Severity Index (PASI)≥10 and Dermatology Life Quality Index (DLQI)>10**

Data collected 6 monthly for first 3 years, annually thereafter

Inclusion criteria

- Data lock October 2016
- Biologic-naive
- Chronic plaque psoriasis
- Follow-up data available

Serious infection defined by association with:

- Hospitalisation and/or;
- Intra-venous anti-microbial therapy and/or;
- Death

***A priori* chosen co-variates**

Demographics: age, gender, body mass index, waist circumference
Lifestyle factors and comorbidities: alcohol intake, smoking status, diabetes, chronic obstructive pulmonary disease (COPD), asthma, immuno-deficiency syndrome (e.g. HIV), number of co-morbidities
Disease severity and treatment: PASI, presence of inflammatory arthritis, concomitant immuno-suppressants for psoriasis (e.g. methotrexate) adjusted for as a time-varying covariate

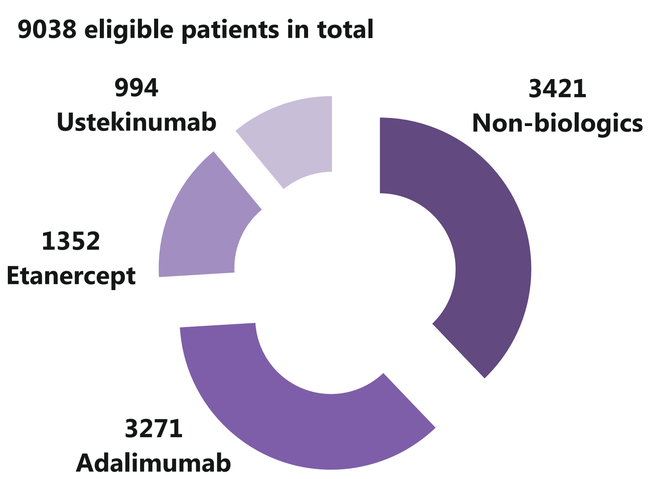
Crude incidence rates calculated for each biologic; non-biologic systemic cohort.

Potential confounding from co-variates controlled for using inverse probability treatment weighting (IPTW) by propensity score generated from a multi-nomial logistic regression model.

Balance between cohorts after weighting assessed using expected bias from a logistic regression model estimating effects of the co-variates on the outcome.

Cox proportional hazards model for hazard ratio (HR) to 1st serious infection; missing data treated with multiple imputation (20 cycles)

RESULTS



Median (IQR) follow-up duration
Non-biologic 1.4 (1.8) year; Adalimumab 2.0 (2.2) years
Etanercept 1.9 (2.6) years; Ustekinumab 2.0 (2.1) years

Figure 1: Number of patients and median follow-up in each cohort

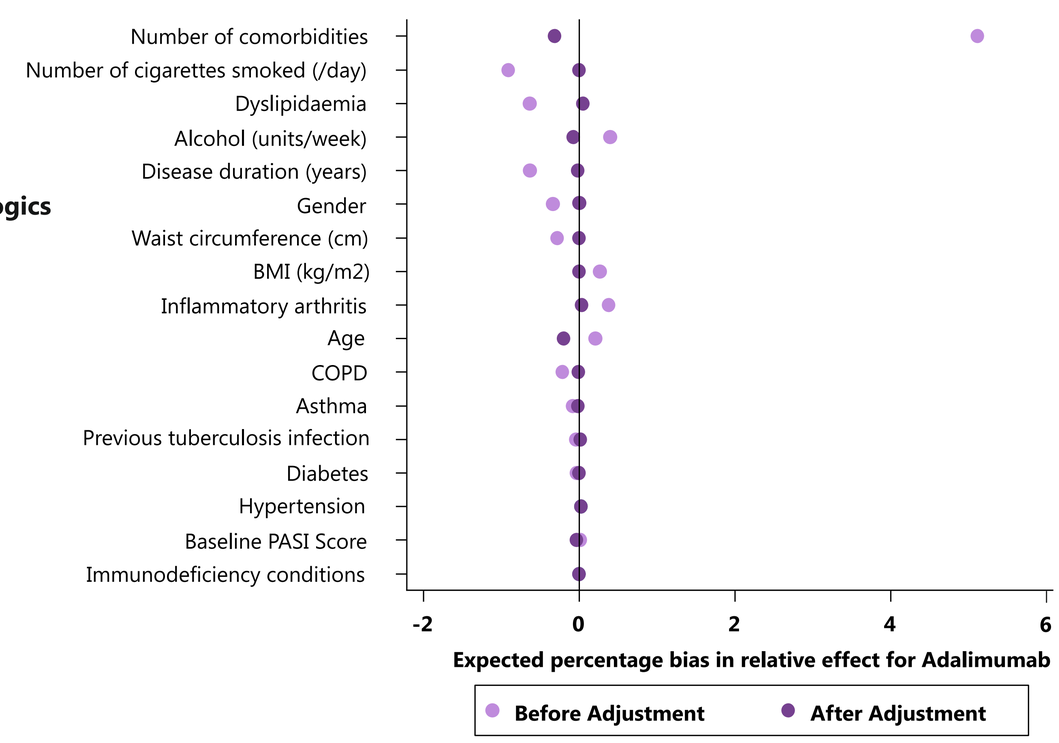


Figure 2: Forest plot showing the reduction in expected percentage bias for the individual co-variates after IPTW propensity score weighting using adalimumab as an example

Treatment	Total Person-time (years)	Infections (n=283)	Rate (/1000 person-years); 95% confidence interval (CI)
Non-biologics	6419.2	91	14.2 (11.5,17.4)
Etanercept	3278.2	50	15.3 (11.6,20.1)
Adalimumab	7835.2	108	13.8 (11.4,16.6)
Ustekinumab	2256.4	34	15.1 (10.8,21.1)

Table 1: Total person-time, number of infections, and crude incidence rate in each cohort

Treatment	Crude HR (95% CI)	Adjusted HR (95% CI)
Etanercept	1.11 (0.79, 1.57)	1.10 (0.75, 1.60)
Adalimumab	0.98 (0.74, 1.29)	0.93 (0.69, 1.26)
Ustekinumab	1.04 (0.70, 1.54)	0.92 (0.60, 1.41)

Table 2: Crude and adjusted effect estimates for the individual biologic therapies against non-biologic therapies from the Cox regression models

DISCUSSION

1. Crude incidence rates of serious infections for etanercept and adalimumab are similar to reported figures; ustekinumab rates are higher than reported figures.
2. Adjusted results similar to PSONET[5] (European collaboration of psoriasis registries)- no increased risk with tumour necrosis factor-α inhibitors compared with acitretin, methotrexate or ciclosporin.
3. Different to results from PSOLAR[6] (US based psoriasis registry which found higher risk with adalimumab compared with acitretin/phototherapy.

Strengths and weaknesses of the study

- ✓ Real-world data
- ✓ Large sample size
- ✓ Detailed data capture
- ✓ Involvement of 153 UK and ROI centres
- ✓ Fully industry independent data analysis
- ✘ Non-randomisation
- ✘ Residual confounding

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.

1 Warren RB *et al.* (2015) *J Invest Dermatol* 135:2632-40. **2** Garcia-Doval *et al.* (2012) *Arch Dermatol* 148:463-70. **3** Yiu ZZ *et al.* (2016) *J Invest Dermatol* 136: 1584-91. **4** Burden AD *et al.* (2012) *Br J Dermatol* 166:545-54 **5** Garcia-Doval *et al.* (2017) *J Am Acad Dermatol* 76:299-308.e16 **6** Kalb RE *et al.* (2015) *JAMA Dermatol* 151:961-9

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