DRUG SURVIVAL OF ADALIMUMAB, USTEKINUMAB AND SECUKINUMAB IN PATIENTS WITH PSORIASIS

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

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SUMMARY

We found that secukinumab and ustekinumab had similar drug survival in the real world, while the drug survival of adalimumab was lower, suggesting that the real world drug survival of secukinumab is higher than previously reported.

We found that psoriatic arthritis and experience of having had previous biologic therapies had differential effects on drug discontinuation in the three biologic cohorts. These predictors may help patients and clinicians choose the most appropriate biologic therapy.

BACKGROUND

1. Patients treated with biologic therapies for psoriasis may have to discontinue treatment and/or switch therapies over time due to loss of effectiveness / the development of adverse events.
2. Drug survival is a proxy measure for effectiveness, safety and tolerability of a medicine. This is defined by duration of time from initation to discontinuation of therapy.
3. Identifying predictors of differential biologic survival may have the potential to help patients and clinicians identify the right biologic first time.
4. Small observational studies showed secukinumab had a lower drug survival than other biologic therapies for psoriasis.

AIM

To report on the drug survival of adalimumab, ustekinumab and secukinumab for psoraisis in the UK and Republic of Ireland; and to identify clinical predictors that affect their drug survival.

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 collected 6 monthly for first 3 years, annually thereafter.

Inclusion criteria: patients with chronic plaque psoriasis starting adalimumab, ustekinumab or secukinumab with follow-up data for 1 year, data lock August 2019.

Discontinuation of therapy defined as any gap in treatment for more than 90 days. Reasons for discontinuation were classified as ineffectiveness, adverse events, or others.

***A priori* chosen co-variates[2]**
age, sex, body mass index (BMI), psoriatic arthritis (PsA)

Variables assessed for inclusion in backward elimination (p = 0.1):
alcohol intake, smoking status, diabetes, chronic obstructive pulmonary disease (COPD), number of co-morbidities, previous biologic exposure status, Psoriasis Area and Severity Index (PASI), needing concomitant use of methotrexate or ciclosporin. waist, nail psoriasis, palmoplantar psoriasis, flexural psoriasis, scalp psoriasis, unstable psoriasis

Biologic drug survival examined using Kaplan-Meier survival analysis. Survival functions at 1 and 2 years were reported. Biologic drug survival was stratified by reasons for discontinuation.

Flexible parametric survival model fitted with outcome of discontinuation due to ineffectiveness utilised as a proxy for biologic treatment failure. Number of knots for restricted cubic spline function to model baseline hazard selected to give the smaller Akaike information criterion and Bayesian information criterion. Three knots and one knot was placed for the restricted cubic splines to model the baseline hazard and the time-dependent effect of biologic treatment respectively.

Selected dichotomous predictors tested for effect modification with biologic therapy on drug discontinuation. Continuous predictors tested for non-linearity and fractional polynomial transformation using the *mfpmi* command in Stata 15.1. BMI = $(BMI/10)^{-2}$ Number of comorbid conditions = $[(no.\ conditions+1)/10]^{-2}$

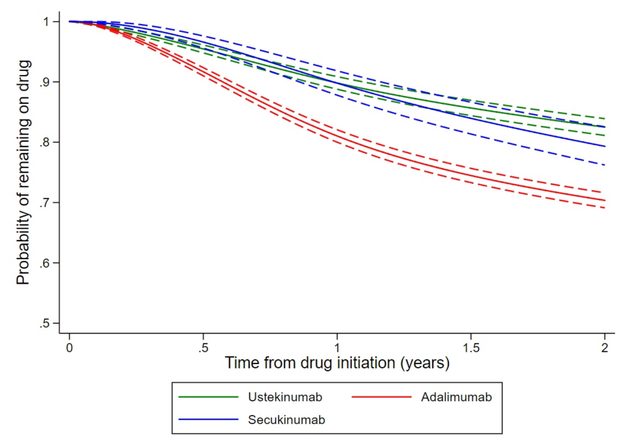
Non-proportionality of the comparative biologic survival tested by comparing two models, one accounting for time-dependent effects of biologic choice, with the likelihood ratio test. Missing data accounted for with 20 multiply imputed datasets.

RESULTS

	Adalimumab (n=5543)		Secukinumab (n=991)		Ustekinumab (n=3118)	
	Total participants / discontinuations	Survival function (95% CI)	Total participants / discontinuations	Survival function (95% CI)	Total participants / discontinuations	Survival function (95% CI)
All reasons						
Year 1	3818/1155	0.78 (0.77-0.79)	510/82	0.88 (0.86-0.91)	2169/330	0.88 (0.87-0.89)
Year 2	2793/556	0.66 (0.64-0.67)	199/53	0.77 (0.73-0.80)	1484/233	0.77 (0.76-0.79)
Ineffectiveness						
Year 1	3818/628	0.87 (0.86-0.88)	510/44	0.93 (0.91-0.95)	2169/156	0.94 (0.93-0.95)
Year 2	2793/301	0.80 (0.78-0.81)	199/28	0.87 (0.84-0.90)	1484/107	0.89 (0.87-0.90)
Adverse events						
Year 1	3818/323	0.93 (0.93-0.94)	510/28	0.96 (0.95-0.97)	2169/103	0.96 (0.95-0.97)
Year 2	2793/143	0.89 (0.88-0.90)	199/12	0.93 (0.91-0.95)	1484/60	0.93 (0.92-0.94)

Table 1: Survival functions at years 1 and 2 for the three biologic cohorts stratified by reason for drug discontinuation

Figure 1: Adjusted survival curve standardising over the covariate pattern for adalimumab, secukinumab and ustekinumab cohorts, with the dotted lines denoting the 95% confidence intervals.



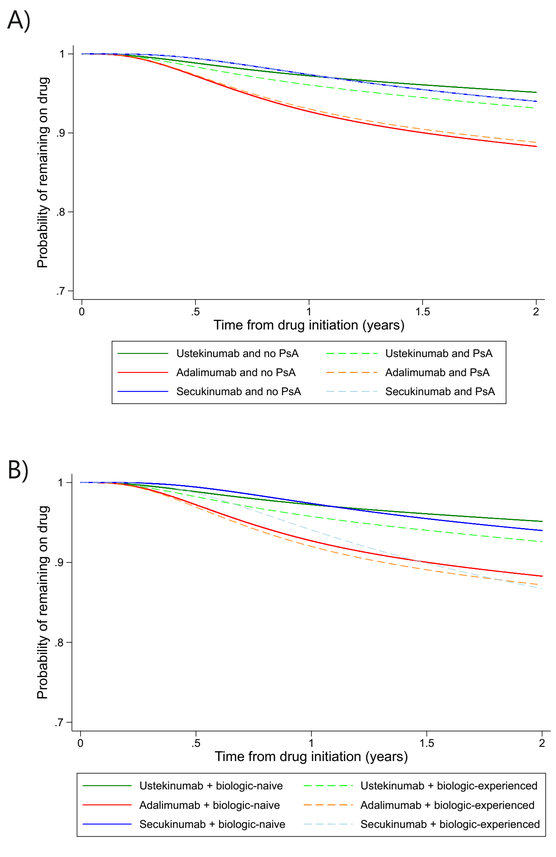
Icons made by Freepik from www.flaticon.com

Covariate	Hazard ratio (95% CI)
Age	1.00 (0.99-1.00)
Female sex	1.28 (1.16-1.42)
Baseline PASI	1.02 (0.84, 1.20
BMI*	0.03 (0.01-1.12)
Number of comorbidities	1.00 (1.00-1.00)
Waist	1.00 (1.00-1.01)
Palmoplantar psoriasis	1.12 (0.99-1.27)
Flexural psoriasis	1.12 (1.01-1.24)
Diabetes	1.34 (1.15-1.57)
Concomitant methotrexate	1.21 (1.03-1.42)
Concomitant ciclosporin	2.53 (1.98-3.22)
Biologic therapies - Ustekinumab	Ref
Adalimumab	2.11 (1.76-2.54)
Secukinumab	0.67 (0.40-1.11)
Psoriatic arthritis (ustekinumab)	1.42 (1.12-1.81)
Psoriatic arthritis (adalimumab)	0.67 (0.51-0.88)
Psoriatic arthritis (secukinumab)	0.70 (0.40-1.24)
Biologic experienced (ustekinumab)	1.54 (1.26-1.89)
Biologic experienced (adalimumab)	0.71 (0.55-0.92)
Biologic experienced (secukinumab)	1.49 (0.91-2.45)

Table 2: Final multivariable prognostic model for drug survival

Figure 2: Predicted survival curves from the flexible parametric model for a typical male patient with psoriasis (age 45 years, BMI 30 kg/m^2, waist 101cm, PASI 20, two other comorbid conditions, no flexural or palmoplantar psoriasis, no diabetes, not on concomitant therapies).

Survival curves for all three biologic therapies in a) typical biologic-naive patient with or without PsA and b) typical patient without PsA who is either the biologic-naive or biologic-experienced.



DISCUSSION

1. This study is the largest study to date investigating the drug survival of secukinumab in patients with psoriasis.
2. We showed that secukinumab has a similar sustained drug survival overall compared with ustekinumab.
3. Both PsA and previous biologic exposure status showed differential effects in the three cohorts for the prediction of discontinuation of therapy due to ineffectiveness, as illustrated in Table 2 and Figure 2.

Strengths and weaknesses of the study

- ✓ Representative sample of patients on secukinumab
- ✓ Detailed data capture including of potential predictors
- ✓ Involvement of 164 UK and ROI dermatology centres
- ✘ 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) Clinical Lectureship.
The views expressed are those of the author and not necessarily those of the NHS, the NIHR, or the Department of Health.

1 Burden AD *et al.* (2012) *Br J Dermatol* 166:545-54 **2** Mourad A *et al.* (2019) *Br J Dermatol* 181:450-8