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Treatment modalities and risk of adverse events associated with biologic therapy: A 10-year observational review of the Australasian Psoriasis Registry

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Ethics Approval statement:

This research project was approved by the governing committee members of the APR and by Belberry Ethics Committee. The APR has been approved to collect data by relevant Human Research Ethics Committees covering the 104 participating sites in Australia and New Zealand, including both public hospitals and privately funded clinics. The lead site of approval was through the Belberry Ethics Committee (HREA-A 131-09) and local ethics approval.

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i. Title:

Treatment modalities and risk of adverse events associated with biologic therapy: A 10-year observational review of the Australasian Psoriasis Registry

ii. Abstract and key words:

Background: Psoriasis is a chronic inflammatory disease affecting ~2-3% of the Australian population. Therapeutic options include topical agents, phototherapy, systemic immunomodulators and biologic agents. Biologics present an acceptable short- and medium-term safety profile, derived mainly from randomised controlled trials(RCTs), however may not represent real world rates of adverse events(AEs).

Methods: A retrospective, observational study of patients enrolled in The Australasian Psoriasis Registry from April 2008-October 2018 was conducted. Data was collected from 104 sites in Australia and New Zealand. Patient characteristics, treatments and AE data were collected. AEs were classified by MedDRA System events.

Results: 2094 patients were included(3765 patient-treatments), comprising; 1110 phototherapy, 1280 systemic and 1375 biologic therapy patient-treatments. Treatment arms were not mutually exclusive. The mean±SD from date of diagnosis of psoriasis to commencement of biologic therapy was 8.9±12.3 years. Methotrexate had the longest exposure time(3740.3 patient-years) and ustekinumab had the longest median (95%CI)time

on treatment, 4.3 years(2.2,6.6). AE differences on biologic treatment were present between patients who would have been eligible or ineligible for RCTs. Approximately 29% of registry patients would have been excluded from clinical trials enrolment. Patients ineligible for RCTs had increased adjusted hazard ratios of: infections and infestations(2.29,95%CI 1.67-3.14;*p*<0.001), cardiac(8.20,95%CI 3.54-25.56;*p*<0.001), gastronintestinal(3.49, 95%CI 1.52-8.01;*p*<0.001), hepatobiliary(5.63,95%CI 1.66-19.11;*p*<0.001), psychiatric(4.67,95%CI 1.54-14.15;*p*=0.006), and eye disorders(4.84,95%CI 151-15.56;*p*=0.008), compared to those eligible for RCTs. Incidence rates in the trial eligible patients were similar to those reported from RCT rates.

Conclusions: This study establishes treatment modalities in use for severe psoriasis and the clinical rates of AEs associated with biologic therapy.

Key words: Psoriasis, Treatment, Biologic therapy, Phototherapy, Systemic therapy, Adverse events, Australia

iii. Main text:

Introduction:

Psoriasis is a chronic, relapsing, inflammatory disease that affects at least 2-3% of the Australasian population, with no predilection for sex.[1] The burden of moderate-to-severe psoriasis has been correlated with other chronic disorders including diabetes, cardiovascular

disease and the metabolic syndrome, in addition to significant psychosocial distress and impaired quality of life.[1] Therapeutic options for psoriasis include topical agents, phototherapy (narrow band ultraviolet light[NB-UVB] and psoralen ultraviolet A[PUVA]), acitretin and systemic immunomodulators (methotrexate and cyclosporine).[2] Newly developed biologic agents including; tumour necrosis factor-α(TNF-α) antagonists (etanercept, infliximab and adalimumab), interleukin (IL)-17A antagonists (secukinumab and ixekizumab), IL-12/23 antagonists (ustekinumab) and IL-23p19 subunit antagonists (guselkumab, tildrakizumab and risankizumab) have been employed to treat moderate-to-severe psoriasis.[2,3]

With these highly targeted and effective biologic therapies, we are at a stage where a 90-100% reduction in Psoriasis Area Severity Index scores(PASI90/100) have become the realistic gold standard in clinical trials and clinical practice.[4] These drugs present an acceptable short-and medium-term safety profile, however, this information is derived mainly from randomised controlled trials(RCTs), their extensions and reporting of adverse reactions.[5,6] These rates may not represent real world clinical practice, as clinical trial participants are selected using inclusion and exclusion criteria that aim to, among their other goals, avoid risks to participants.[7] When drugs are approved and prescribed in clinical practice, they are administered to a more varied patient population, including groups with comorbidities and confounding factors who are unlikely to be represented in RCTs and for whom RCT results on efficacy and safety might not apply.[7,8] Of note, >30% of patients in clinical practice and registries have risk factors that would preclude them from enrolment in clinical trials.[3,7,9]

This paper utilises data from the Australasian Psoriasis Registry to (1) assess patient characteristics and treatment modalities used over a 10-year period for Australasian psoriasis patients (2) determine which biologic agents were in use over this time and their associated treatment courses and (3) establish the overall rate of adverse events(AEs) associated with biologic therapies in clinical practice and determine if these rates compare to those eligible for RCTs and the reported AE rates from published RCTs.

Materials and Methods:

The Australasian Psoriasis Registry was established in 2008 and includes data from Australian and New Zealand patients with psoriasis. It is a longitudinal, prospective, observational cohort registry that follows psoriasis patients, treated with phototherapy, systemic therapy and/or biologic therapy. The aim of the registry is to collect long-term clinical data relevant to drug safety, efficacy and use of treatment modalities in patients with psoriasis.

A retrospective observational review of the Australasian Psoriasis Registry data from April 2008-October 2018 was undertaken. The registry has been approved to collect data by the relevant Human Research Ethics Committees covering the 104 participating sites in Australia(99 sites) and New Zealand (5 sites), including both public hospitals and private clinics (Belberry Ethics Committee HREC-A131-09). These data are collected by dermatologists or delegated staff members. Patients provide signed informed consent for information collection and registry inclusion. Participation is entirely voluntary. Patients were primarily added to the registry at the time of their first consultation with a dermatologist or when first commencing a biologic agent; this visit also typically included their baseline PASI score. At subsequent visits, emergent AEs were recorded. All registry patients were included, except those that were missing full demographic data or psoriasis type and/or treatment. Demographic information, treatments used, and AEs were collected.

All registry patients who were commenced on biologic therapy had failed to achieve an adequate response to prior treatment as demonstrated by a whole body PASI score of >15; or had psoriasis on the face, palm or hand(s) or sole of the feet where at least 2 of the 3 PASI symptom sub-scores for erythema, thickness and scaling were rated as severe, or the skin affected was ≥30% of the face or palm of a hand of sole of a foot as per the Australian pharmaceutical benefits scheme and the New Zealand Pharmaceutical Management Agency. These governing bodies provide subsidised costs to medications for Australian and New Zealand residents. Biologics patients must have failed to achieve an adequate response to at least 2 of the 4 following treatments (prior to May 2019 this was 3 of the 4): phototherapy(UVB/PUVA, minimum 3 treatments/week), methotrexate(≥10mg/week), cyclosporine(≥2mg/kg/day) or acitretin(≥0.4mg/kg/day) for a minimum of 6 weeks per

therapy; or have a contraindication; or intolerance/toxicity.[8] For New Zealand patients, a similar criteria are required (inadequate response or intolerable side effects to at least three of the following; phototherapy, methotrexate, cyclosporin, or acitretin) and a PASI score >15 was required for access to infliximab, whilst etanercept, adalimumab and secukinumab required PASI scores >10.

An AE was defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment".[10] A treatment course was defined as the time between the first drug administration until twice the drug's half-life after the final dose/drug withdrawal/point of data collection(which ever came first). All biologic agents were categorised separately from oral systemic agents to allow for analyses. A 'patient-treatment' was defined as the total period of one medication used per patient. Given that patients could have concurrent treatment modalities or that patients treated with biologic therapy required a failure of other treatment modalities prior, treatment groups were not deemed mutually exclusive. Only PASI scores from patients with whole body psoriasis were included. Patient ineligibility for RCTs was based on exclusion criteria from international phase 3 comparator clinical trials.[11-15] A list of the exclusion criteria can be found in supplementary Table S1.

Statistical analysis

Summary statistics are presented as mean and standard deviation(SD). To calculate rates, we counted all AEs within each group and used exposure time as the total exposure to the drug group. If one event was linked to several drug exposures, we counted the AE in both groups. The AE analysis was performed for biologics patients only. We obtained crude and age/sex adjusted hazard ratios with 95% confidence intervals(95%CI) for specific AEs (classified by MedDRA System Organ Class[16]) by comparing AE rates between those eligible and ineligible for RCT. The Andersen-Gill model was used, allowing for multiple failures per subject and robust standard errors to consider clustering of AEs in the same patient using Stata Statistical Software: Release 15.0 (College Station,TX, USA: StataCorp LP).

Results:

Patient characteristics

Over the 10-year study period, 2352 patients(Australian n=2271, New Zealander n=81) were registered into the Australasian Psoriasis Registry database, with 316(13.4%) excluded due to lack of demographic or initial treatment data available at the time of analysis. Among the 3765 patient-treatments (2094 patients,37% female), there were 1110 phototherapy, 1280 classic systemic and 1375 biologic therapy patient-treatments registered. Patient demographics, psoriasis sub-type and comorbidities at time of registry database registration by treatment group/class are presented in Table 1. The mean baseline PASI score for each treatment group was similar.

The mean±SD duration of disease (onset of psoriasis symptoms) until the start of treatment was shortest for phototherapy (14.4±11.7 years) and systemic therapy (15.6±11.8 years) compared to biologic therapy (19.3±12.3 years)(p <0.01). The mean±SD from date of diagnosis (by a medical practitioner) to commencement of biologic therapy was 8.9±12.3 years. Ineligibility for RCTs was similar for the phototherapy group(29.8%) compared to classic systemic therapy(29.2%) and biologic therapy(28.4%). A breakdown of rates of patient ineligibility for RCTs based on registry comorbidities can be found in supplementary Table S2. All treatment groups contained patients with a range of comorbidities, with similar rates amongst groups, including those on biologic therapy. Approximately 95% of patients had generalised plaque psoriasis, with more than 50% diagnosed with a body mass index ≥30kg/m², one quarter with hypertension, and >10% with diabetes mellitus (double the prevalence of diabetes in the Australian population) across all treatment groups. All treatment groups contained ~2% of patients that identified as previously or currently positive for hepatitis B, hepatitis C and/or human immunodeficiency virus.

Treatment courses and exposure time

The date of medication listing on the Pharmaceutical Benefits Scheme, drug treatment courses, exposure time and median years on treatment for psoriasis patients from the Australasian Psoriasis Registry are presented in Table 2. NB-UVB phototherapy had the most frequent number of treatment courses, which is consistent with the intermittent use of phototherapy by patients throughout the year (ie. use in winter) and/or use in addition to systemic therapies. Methotrexate had the most frequent number of treatment courses

amongst systemic agents and overall had the longest exposure time (3366.09 patient-years). Of note, 27% of patients who received biologic therapy had concurrently taken methotrexate at some point during their biologic treatment (overlapping treatment courses). Amongst the biologic agents, ustekinumab had the most frequent number of treatment courses (673) and exposure times (3005.14 patient-years), closely followed by the TNF-α antagonists; adalimumab (601 treatment courses; 2618.11 patient-years) and etanercept (390 treatment courses;1543.03 patient-years) respectively. Tildrakizumab and guselkumab had the shortest number of treatment courses representing the small number of patients who received compassionate supply provided by the corresponding pharmaceutical companies, given their lack of approval for government subsidy during the analysis period. Methotrexate had the longest median time(q1,q3) on treatment of 1.0 years(0.2,4.2) for systemic agents, whilst for biologic agents, ustekinumab and adalimumab had the longest median time(q1,q3) on treatment of 4.3 years(2.2,6.6) and 3.9 years(1.1,7.2), respectively.

Adverse events in those receiving biologics

Of importance to this analysis were the rates of AEs observed amongst psoriasis patients treated with biologic therapy, particularly between those assessed as eligible or ineligible for RCTs(Table 3). It was noted that of the MedDRA diagnostic groups of AEs, infections and infestations had the highest proportion of AEs amongst both those eligible (20.1%) and ineligible (45.5%) for RCTs. Infection and infestations AE incidence rates were higher for RCT ineligible patients compared to eligible patients (adjusted HR 2.29,95%CI 1.67-3.14;p<0.001), with a two-fold increase in incidence rate.

Cardiac disorders were reported in 0.5% of RCT eligible and 4.9% of RCT ineligible patients. Of the RCT eligible acute myocardial infarction accounted for 20% and NS chest pain and arrhythmias 80%, whilst the RCT ineligible group consisted of acute myocardial infarctions (61%) and a small number of other cardiac related conditions (arrhythmias, hypertension and acute coronary syndrome) (adjusted HR8.20; 95%CI 2.94-22.88;p<0.001). Similarly, eye disorders amongst RCT eligible patients (conjunctivitis, blurred vision and not specified), showed lower AE rates and less severe AEs compared to ineligible patients (uveitis, optic neuritis, conjunctivitis and not specified) (adjusted HR4.84;95%CI 1.51-15.56;p=0.004).

Significant adjusted HRs for gastrointestinal (3.49; 95%CI 1.52-8.01;*p*<0.001) and hepatobiliary (5.63; 95%CI 1.66-19.11;*p*=0.006) disorders were noted, comprising predominantly diarrhoea/gastroesophageal reflux and liver enzyme elevation/hepatotoxicity respectively. A significant adjusted HR was noted for psychiatric disorders between ineligible and eligible groups (adjusted HR4.67;95%CI1.54-14.15;*p*=0.006), consisting of anxiety, psychosis, depression and suicidal ideation. Neoplastic disease (benign, malignant and unspecified) was noted to account for 15.0% and 25.6% of the proportion of AEs within those eligible and ineligible for RCTs respectively, with no increased risk of malignancy between groups (p=0.501).

Discussion:

Patient demographics

In the registry cohort there was a high rate of ineligibility for RCTs noted for phototherapy, systemic therapy and biologic agent treatment groups of 29.8%, 29.2% and 28.4% respectively. Our eligibility rates were similar to those reported in a Spanish national registry who noted 32.2% and 27.8% ineligibility for RCTs for classic systemic therapy and biologic therapy respectively.[6] The highest rates of ineligibility were due to patients with a history or current signs of severe systemic disease(16.1%) and those with a known malignancy or history of malignancy within the 5 years prior to commencement of therapy (6.8%)(Table S2). The ineligibility rates may be higher for patients using phototherapy and systemic agents because of confounding issues that may have prevented them from progressing to a biologic agent.[17]

The assessment of the registry mean baseline PASI scores from all three groups indicated scores well above a PASI of 12 (mean of 21.4±9.3), indicating severe psoriatic disease in our cohort.[18,19] Our analysis revealed a high prevalence of obesity, hypertension and hyperlipidaemia among all treatment groups, in concordance with other psoriasis registries[20,21] and confirming the association between psoriasis and risk of obesity, poorly controlled hypertension and a significant association between psoriasis severity and dyslipidaemia.[22] We also recorded high levels of diabetes mellitus, which is an important consideration when treating psoriasis patients, given that diabetic patients with psoriasis are more likely to require pharmacological management, and to suffer micro- and

macrovascular diabetic complications compared to diabetic patients without psoriasis.[22,23] We noted low levels of psychiatric illness at baseline. We expected a much higher prevalence given other registry data and the well-documented association between severe psoriasis and increased rates of depression, anxiety and suicidality compared to the general population.[20-22] These low levels may be explained by patients wanting to explore their mental health issues with their primary care physician instead of their dermatologist, or due to incomplete interpretation of the Dermatology Life Quality Index scores, which may not identify clinically important levels of anxiety and depression.[24] Within the biologics group, RCT ineligible patients had higher rates of psychiatric illness compared to eligible patients, indicating that patients within clinical practice(especially those with significant comorbidities) may require more intensive psychiatric screening, evaluation and management.[24]

Current treatment modalities

Methotrexate was noted to have the most frequent number of treatment courses and longest exposure time for registry patients. This may suggest its high efficacy, low cost, relative ease of administration and usefulness in concomitant psoriatic arthritis, since its early approval onto the Pharmaceutical Benefits Scheme in 1973.[27] There is also mounting evidence for the use of methotrexate as a concomitant treatment for patients on a biologic agent due to its immunomodulatory and anti-inflammatory effects, and synergism with biologics, as well as purported prevention of antidrug antibodies.[28] We noted that 27% of biologics patients had been administered methotrexate concurrently during their biologic treatment. Thus, an ongoing awareness of the hepatotoxic side effects of methotrexate are required, especially as psoriasis has been associated with a higher prevalence of chronic hepatitis and alcoholic/non-alcoholic fatty liver disease (OR 1.41;95%CI 1.12–1.76).[22] This was reflective in our registry cohort, with a baseline rate of ~9-10% of patients with liver disease.

Ustekinumab (approved on the Pharmaceutical Benefits Scheme since 2010) was noted to have the longest median number of years on treatment compared to other biologic agents. It has been indicated for chronic plaque psoriasis, psoriatic arthritis and inflammatory bowel disease, which may contribute to its combined success in patients with multiple

comorbidities.[8] It has also been shown to have good long-term efficacy and low comparable cumulative incidence rate of AEs with 12-weekly dosing and increased dosing for patients weighing >100 kg.[29] We noted relatively low use of newer agents such as guselkumab and tildrakizumab, given their recent inclusion into the Australasian markets.[8]

Adverse events associated with biologics

In patients receiving biologic treatment, we noted the risk of AEs was higher for those ineligible for RCTs compared to eligible patients. Adjusted HRs by diagnostic groups, showed that patients on biologics who were assessed as ineligible for RCTs had an increased risk of infections and infestations, musculoskeletal and connective tissue disorders, cardiac disorders, gastrointestinal disorders, hepatobiliary disorders, psychiatric disorders and eye disorders compared to eligible patients. The proportion of AEs for infections and infestations was 20.1% for RCT eligible and 45.5% ineligible biologics patients. These levels were higher than those previously reported by Carretero *et al*.,(2015) in clinical practice with an AE frequency of 20.7% for infections.[7]

All grouped AEs observed in those eligible for RCTs from our registry were higher than those recorded in published RCTs[11-14] and similar to other registries.[30] Registrational RCT study and follow-up times ranged from 16-56 weeks, which may account for the lower incidence rates noted in RCTs compared to longer observation periods in our registry. All RCTs reported observational rates of nasopharyngitis, upper respiratory tract infections and localised mucosal or cutaneous *Candida* infections (particularly anti-IL17 biologics) in treatment groups that were higher than placebo(p<0.001). We were not able to compare these values exclusively given non-specific recording of infections and infestations. It has been noted in RCTs that there were no significant differences in the overall proportion (<1%) of major cardiac AEs between treatment groups.[11,12] Registry data also supports this safety observation.[30] Furthermore, similar incidences of cardiac events were noted between participants who completed RCTs and biologics patients within our registry who were eligible for RCTs. Two RCTs noted that exposure-adjusted malignancy rates were low and showed no clinically meaningful differences across treatment groups (secukinumab/etanercept) and placebo groups.[12] We also noted low rates of malignancy within our registry cohort, with no statistical difference between eligibility sub-groups. We

observed a high incidence of AEs involving eye disorders in both biologic eligibility sub-groups but were not able to determine these rates from previous RCTs.

Limitations

The Australasian Psoriasis Registry is an opt-in database and information is freely provided from patients regarding current comorbidities and previous treatments used. A screening checklist of possible comorbidities at time of registration was not compulsory, thus true rates of comorbidities may be higher. It must be noted that patients receiving biologics within the registry had PASI scores >15 (or >10 for New Zealand patients, excluding infliximab), which differs from clinical trial eligibility (PASI≥12) and other registries and should be noted when comparing results. There was potential selection bias in providing a complete case analysis as 13.4%(n=316) patients from the registry were missing key data including psoriasis phenotype, demographic data and/or treatment. AEs may be under-represented as dermatology visit schedules may be every 3-6 months for stable patients, reflecting possible recall bias of AEs. Treatment groups were not mutually exclusive. We grouped all AEs from individual biologic drugs and systemic agents under either biologics or systemics, thus information on individual drug AEs were not available for analysis.

We provide evidence that RCTs provide information that is representative of most, but not all patients seen within dermatology clinical practice. Registries are important to collect longer term data and real-life use of treatment, particularly in patients with psoriasis. Registries include patients who would not qualify for inclusion in RCTs, which has been reported previously and confirmed in this study. AE types were similar between those who would have been eligible or ineligible for RCTs. Furthermore, AEs occurred more frequently in the RCT ineligible group, providing further reason to collect data from this group. We advocate for increased vigilance in the management of psoriasis patients on biologics, especially those with significant comorbidities. Given the changing landscape of treatment in psoriasis, an ongoing comprehensive registry will be required for dynamic assessment of patients.

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TABLE 1: Baseline characteristics of psoriasis patients from the Australasian Psoriasis Registry by treatment group/class

	Phototherapy	Classic Systemic Therapy	Biologic Therapy
Demographic data			
Number of patient-treatments, n (%)	1110 (47.0)	1280 (61.1)	1375 (65.7)
Female sex, n (%)	428 (38.2)	473 (37.0)	504 (36.7)
Age, years, mean (SD)	51.8 (14.5)	53.0 (13.9)	53.1 (13.5)
Duration of disease at start of treatment, years, mean (SD)	14.4 (11.7)	15.6 (11.8)	19.3 (12.3)
Psoriasis Area Severity Index (PASI), mean (SD)	24.1 (9.3)	24.1 (9.0)	24.7 (9.0)
Ineligible for RCTs	331 (29.8)	374 (29.2)	391 (28.4)
Family history of psoriasis	449 (40.1)	506 (39.5)	517 (37.6)
Psoriasis sub-type at registration, n (%)			
Generalised plaque psoriasis	1038 (93.5)	1221 (95.4)	1311 (95.3)
Palmoplantar psoriasis	155 (14.0)	184 (14.4)	187 (13.6)
Guttate psoriasis	84 (7.6)	61 (4.8)	49 (3.6)
Generalised pustular psoriasis	32 (2.9)	36 (2.8)	35 (2.5)
Erythrodermic psoriasis	11 (1.0)	11 (0.9)	12 (0.9)
Psoriatic arthritis	349 (31.4)	441 (34.5)	475 (34.5)
Co-morbidities at registration, n (%)			
Obesity (BMI≥30kg/m^2)	597 (50.6)	726 (56.7)	783 (57.0)
Hypertension (SBP ≥140mmHg)	270 (24.1)	337 (26.3)	349 (25.4)
Hyperlipidaemia	223 (19.9)	278 (21.7)	284 (20.7)
Diabetes Mellitus	137 (12.2)	161 (12.6)	169 (12.3)
Liver Disease	110 (9.8)	123 (9.6)	130 (9.5)
Non-Melanoma Skin Cancer	102 (9.1)	126 (9.8)	143 (10.4)
Ischaemic heart disease	56 (5.0)	67 (5.2)	72 (5.2)
Psychiatric Illness	53 (4.7)	53 (4.1)	60 (4.4)
Other Cancer	52 (4.6)	57 (4.4)	60 (4.4)
Alcoholism	26 (2.3)	29 (2.2)	34 (2.5)
Cutaneous Melanoma	19 (1.7)	37 (2.9)	34 (2.5)
Bowel Disease	16 (1.4)	16 (1.3)	20 (1.5)
History of Tuberculosis	13 (1.2)	16 (1.3)	15 (1.1)
Lupus	8 (1.0)	9 (0.7)	9 (0.7)

Chronic heart failure	6 (1.0)	9 (0.7)	10 (0.7)
Uveitis	3 (0.3)	2 (0.2)	3 (0.2)
Spondylitis	5 (0.4)	5 (0.4)	7 (0.5)
Hepatitis B	9 (0.8)	9 (0.7)	9 (0.7)
Hepatitis C	10 (0.9)	12 (0.9)	15 (1.1)
Human immunodeficiency virus	4 (0.4)	4 (0.3)	4 (0.3)

SD = Standard deviation; RCT = randomised controlled trials; BMI = Body mass index; SBP = Systolic blood pressure; Duration of disease = onset of psoriasis symptoms until treatment

Table 2: Description of treatment courses and exposure time for psoriasis patients from the Australasian Psoriasis Registry

Treatment	Date of PBS Approval	Number of treatment courses (%)	Exposure time in patient-years	Median years on treatment (q1, q3)
Phototherapy				
NB-UVB	MBS	1087 (96.5)	2547.28	0.8 (0.2, 3.1)
PUVA	MBS	39 (3.5)	94.10	1.2 (0.3, 2.0)
Classic Systemics				
Methotrexate	Aug 1973	1123 (42.4)	3366.09	1.0 (0.2, 4.2)
Acitretin	Aug 1995	864 (32.6)	1241.01	0.3 (0.1, 1.2)
Cyclosporin	Mar 1996	663 (25.0)	710.01	0.3 (0.1, 1.0)
Biologic agents				
Etanercept	Aug 2006	390 (16.7)	1543.03	2.3 (0.7, 7.1)
Infliximab	Dec 2007	251 (10.7)	1217.54	3.4 (1.2, 8.8)
Adalimumab	Jun 2009	601 (25.7)	2618.11	3.9 (1.1, 7.2)
Ustekinumab	Mar 2010	673 (28.8)	3005.14	4.3 (2.2, 6.6)
Secukinumab	Sep 2015	268 (11.5)	668.72	2.6 (1.5, 3.3)
Ixekizumab	Feb 2017	100 (4.3)	150.74	1.1 (0.8, 2.1)
Guselkumab*	Feb 2019	41 (1.8)	26.26	0.7 (0.6, 0.8)
Tildrakizumab*	Feb 2019	14 (0.6)	8.23	0.6 (0.6, 0.7)

PBS = Pharmaceutical Goods Scheme; NB-UVB = Narrow band Ultraviolet B phototherapy; PUVA = Psoralen ultraviolet A; MBS = Medicare Benefits Schedule rebate

* These agents were supplied under compassionate supply from the sponsor

Table 3: Adverse events of psoriasis patients treated with biologic therapy from the Australasian Psoriasis Registry based on eligibility for randomised controlled trials.

Biologic Therapy	Eligible for RCT				Ineligible for RCT				Eligible versus Ineligible for RCT		
	Cases (n)	Proportion of AEs (%)	Total person-years ('000)	Incidence per 1000py (95%CI)	Cases (n)	Proportion of AEs (%)	Total person-years ('000)	Incidence per 1000py (95%CI)	Crude hazard ratio (95%CI)	Adjusted* hazard ratio (95%CI)	P-value
Rates for MedDRA Diagnostic Groups of adverse events											
Infections and infestations	198	20.1	6.12	32.34 (28.1,37.2)	178	45.5	2.33	76.41 (66.0, 88.5)	2.36 (1.72-3.25)	2.29 (1.67-3.14)	**<0.001**
Neoplasms: benign, malignant and unspecified	148	15.0	6.34	23.35 (19.9, 27.4)	100	25.6	2.50	40.08 (32.9, 48.8)	1.82 (1.08-3.09)	1.20 (0.71-2.01)	0.501
Skin and subcutaneous tissue disorders	41	4.2	6.43	6.37 (4.7, 8.7)	19	4.9	2.60	7.30 (4.7, 11.4)	1.17 (0.68-2.02)	1.24 (0.72-2.11)	0.439
Nervous system disorders	16	1.6	6.53	2.45 (1.5, 4.0)	8	2.0	2.64	3.03 (1.5, 6.1)	1.17 (0.43-3.22)	1.16 (0.44-3.05)	0.764
Musculoskeletal and connective tissue disorders	17	1.7	6.50	2.61 (1.6, 4.2)	19	4.9	2.60	7.32 (4.7, 11.5)	2.81 (1.40-5.66)	2.69 (1.32-5.50)	**0.007**
Blood and lymphatic system disorders	8	0.8	6.53	1.22 (0.6, 2.5)	8	2.0	2.63	3.04 (1.5, 6.1)	2.53 (0.94-6.79)	2.07 (0.79-5.44)	0.141
Cardiac disorders	5	0.5	6.53	0.77 (0.3, 1.8)	19	4.9	2.60	7.30 (4.7, 11.4)	9.51 (3.54-25.56)	8.20 (2.94-22.88)	**<0.001**
Gastrointestinal disorders	11	1.1	6.51	1.69 (0.9, 3.1)	16	4.1	2.60	6.15 (3.8, 11.0)	3.71 (1.71-8.04)	3.49 (1.52-8.01)	**<0.001**
General disorders and administration-site disorders	32	3.3	6.49	4.93 (3.5, 7.0)	26	6.6	2.58	10.06 (6.8, 14.8)	2.09 (1.14-3.83)	2.03 (1.10-3.73)	**0.023**
Hepatobiliary disorders	4	0.4	6.53	0.61 (0.2, 1.6)	10	2.6	2.62	3.81 (2.1, 7.1)	6.56 (2.06-20.88)	5.63 (1.66-19.11)	**0.006**

Immune System disorders	11	1.1	6.54	1.68 (0.9, 3.0)	8	2.0	2.64	3.03 (1.5, 6.1)	1.84 (0.74-4.58)	1.66 (0.69-4.00)	0.260
Injury, poisoning, and procedural complications	2	0.2	6.54	0.31 (0.1, 1.2)	3	0.8	2.64	1.14 (0.4, 3.5)	3.88 (0.64-23.37)	4.91 (0.74-32.38)	0.098
Psychiatric disorders	4	0.4	6.54	0.61 (1.2, 1.6)	6	1.5	2.63	2.28 (1.0, 5.1)	3.85 (1.09-13.62)	4.67 (1.54-14.15)	**0.006**
Respiratory, thoracic and mediastinal disorders	6	0.6	6.52	0.92 (0.4, 2.0)	7	1.8	2.63	2.66 (1.3, 5.6)	2.89 (0.98-8.57)	2.37 (0.78-7.26)	0.129
Vascular disorders	8	0.8	6.52	1.23 (0.6, 2.5)	9	2.3	2.62	3.44 (1.8, 6.6)	2.82 (1.09-7.27)	2.22 (0.88-5.60)	0.091
Metabolism and nutrition disorders	9	0.9	6.50	1.38 (0.7, 2.7)	3	0.8	2.64	1.14 (0.4, 5.3)	0.83 (0.23-3.09)	0.92 (0.21-4.00)	0.908
Renal and urinary tract disorders	4	0.4	6.53	0.61 (0.2, 1.6)	8	2.0	2.62	3.05 (1.5, 6.1)	4.99 (1.46-17.06)	3.88 (1.18-12.76)	**0.026**
Pregnancy	24	2.4	6.50	3.69 (2.5, 5.5)	8	2.0	2.63	3.04 (1.5, 6.1)	0.83 (0.30-2.28)	1.31 (0.48-3.55)	0.600
Melanoma (*in situ* and invasive)	7	0.7	6.52	1.07 (0.5, 2.2)	4	1.0	2.63	1.52 (0.6, 4.1)	1.42 (0.42-4.81)	0.96 (0.27-3.44)	0.944
Eye disorders	5	0.5	6.53	0.77 (0.3, 1.8)	9	2.3	2.64	3.41 (1.8, 6.6)	4.48 (1.51-13.33)	4.84 (1.51-15.56)	**0.008**
Surgical and medical procedures	6	0.6	6.52	0.92 (0.4, 2.0)	8	2.0	2.61	3.06 (1.5, 6.1)	3.38 (1.11-10.29)	2.64 (0.83-8.42)	0.102

*Adjusted for age and sex of patients between groups; AE = Adverse event; CI = Confidence Interval; RCT = Randomised Controlled Trial; 1000py = 1000 person-years