Cumulative exposure to biologics and risk of cancer in psoriasis patients

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Cumulative exposure to biologics and risk of cancer in psoriasis patients: a meta-analysis of Psonet studies from Israel, Italy, Spain, United Kingdom and Republic of Ireland

Running head: Risk of cancer and biologic psoriasis therapy.

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Conflict of interest:

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Keywords: Psoriasis, biologic agents, systemic agents, immunosuppressive agents, safety, anti-TNF, cancer.

Bulleterd statements:

What is already known about this topic?

- Systemic therapies, including biologics, are widely prescribed for patients with moderate-to-severe psoriasis.
- Due to the immunomodulatory mechanism of biologic therapies for psoriasis, it is hypothesized that long-term exposure to them may increase the risk of developing cancer.

What does this study add?

- This study suggests that treatment of psoriasis patients with biologics in current clinical practice is not associated with an increased risk of cancer in the medium-term, after a few years of use and latency.
- Given the heterogeneity of the data sources and methodological limitations, it remains unclear if use of biologics may be associated with an increased (albeit small) risk of certain cancer subtypes.

ABSTRACT

Background: Cancer risk following long-term exposure to systemic immunomodulatory therapies in psoriasis patients is possible.

Objectives: To assess a dose-response relationship between cumulative length of exposure to biologic therapy and risk of cancer.

Methods: Four national studies (a healthcare database from Israel, and prospective cohorts from Italy, Spain and UK/ROI) collaborating through Psonet (European Registry of Psoriasis) participated in these nested case-control studies, including nearly 60,000 person-years of observation. Cases were patients who developed an incident cancer. Patients with previous cancers and benign or *in-situ* tumours were excluded. Four cancer-free controls were matched to each case on year of birth, gender, geographic area, and registration year. Follow-up for controls was censored at the date of cancer diagnosis for the matched case. Conditional logistic regression was performed by each registry. Results were pooled using random effects meta-analysis.

Results: 728 cases and 2671 controls were identified. After matching, differences between cases and controls were present for the Charlson comorbidity index in all three registries, and in the prevalence of previous exposure to psoralen-ultraviolet-A (PUVA) and smoking (BADBIR only). The risk of first cancers was not significantly associated with cumulative exposure to biologics (adjusted odds ratio per year of exposure 1.02; 95%CI 0.92, 1.13). Results were similar if squamous and basal cell carcinomas were included in the outcome.

Conclusion: Cumulative length of exposure to biologic therapies of psoriasis patients in real-world clinical practice does not appear to be linked to a higher risk of cancer after several years of use.

INTRODUCTION

Since the introduction of biologic therapy for treating moderate-to-severe psoriasis, some concerns remain about their possible long-term safety. As immunomodulatory drugs, they could theoretically increase the risk of cancer in patients. Previous data, including spontaneous reports, data from clinical trials and observational studies, gave inconclusive results. A recent systematic review provided signals of an increased cancer risk in all psoriasis patients and in those exposed to anti-TNFs (particularly linked to squamous cell carcinoma (SCC)), but the increased risk might be due to inadequate control of key confounding factors (Ultraviolet exposure (UV), previous cancers and smoking) or use of historic controls¹⁻³.

Detecting an increased risk of cancer is difficult as it is a rare outcome and most studies are underpowered to detect small increases in risk, especially if there is a need to control for confounding as in observational studies. A long latency time to the development of cancer adds to the difficulty of answering this question. Immunosuppressed patients, such as those who undergo organ transplants, have an elevated incidence of cancers in the years following surgery with complex patterns of incidence over time, most showing an early increase of risk and remaining over time^{4,5}. Registries included in Psonet, a network of pharmacovigilance cohorts and healthcare databases investigating the safety of biologic therapy in patients with moderate-to-severe psoriasis, have been collecting data for more than 6 years; it might now be possible to detect whether there is an increased risk of cancer. Previous studies have shown that single registries are underpowered to estimate risks of this magnitude¹, which highlights the need for combining the results of several studies⁶.

Our aim was to describe if, in patients with psoriasis requiring systemic therapy, there is a dose-response effect linking cumulative exposure to biologics with a higher risk of cancer.

MATERIALS AND METHODS

Psonet network and participating registries

Psonet comprises independent pharmacovigilance registries and healthcare databases that collaborate to investigate the long-term safety and effectiveness of biologic and systemic therapies in patients with moderate-to-severe psoriasis.

Four Psonet studies provided data for this study: The British Association of Dermatologists Biologic Interventions Register (BADBIR), the Spanish Registry of Systemic Therapy in Psoriasis (Biobadaderm), Clalit Health Service Database and the Italian Registry of Systemic Therapy in Psoriasis (Psocare). Individual data sharing was not feasible due to data ownership restrictions and administrative differences in the databases. All of them have been previously described⁶⁻⁹. Briefly, BADBIR, Biobadaderm and Psocare are prospective pharmacovigilance registries of psoriasis patients receiving biologic and/or systemic therapies followed-up during their healthcare visits or at least once a year. Clalit Health Service database contains the electronic medical records of health services including prescriptions provided by the main health service provider in Israel, with more than 4.4 million enrollees (52% of Israel population). The participating registries agree with the Declaration of Helsinki and received approval by local ethics committees (BADBIR: NHS Research Ethics Committee North West England, reference 07 /MRE08 /9; Biobadaderm: H 12 de Octubre, 216/07; Psocare: locally approved by each participating hospital, Clalit: use of routine data authorized by Clalit IRB 10044, 002/2014, 65/09).

We used a nested case-cohort study as it has advantages for the study of cancer¹⁰ and allowed for homogeneous analysis in all sub-studies given the differences in design and the low number of outcomes. Given that controls sampling was time-matched and cases incident, the odds ratio is an unbiased estimate of the rate ratio.^{11,12}

Defining Cases and Controls

Nested case-control studies within each registry were used to determine the risk of cancer associated with cumulative exposure to biologic therapy. BADBIR, Biobadaderm and Psocare used Medical Dictionary for Regulatory Activities (MedDRA) coding to classify tumours; Clalit used the 10th revision of the International Classification of Diseases (ICD-10). BADBIR also links in to NHS Digital Cancer data. Cases were identified as patients with incident cancers excluding those with a history of cancer, and benign and *in-situ* tumours. All cases were reviewed by each participating group to ensure exclusion of benign and *in-situ* tumours followed by a blind review by two clinicians of the Psonet group (IGD and LN). Patients with basal cell carcinoma (BCC) and SCC were not included in the main dataset (MD) for analysis but were included in two sensitivity analyses (MD+SCC; MD+SCC+BCC; summarised in Table 1). Up to four cancer-free patients in each cohort were matched to each case using closest match to year of birth, sex, registration hospital or health area (all registries), and year of entry in the cohort (BADBIR, Biobadaderm, Psocare). These criteria were selected as they were common to each registry and because they might fulfil the requirements of confounders: being associated with cancer and exposure and not in the causal pathway. Year of entry was included to maximise matching on follow-up time and possibly latency between cases and controls. Due to data ownership issues, it was not possible to provide a breakdown of the number of patients with different types of cancer outside of the pre-agreed SCC and BCC sensitivity analyses for each registry.

Exposure to systemic therapies

Exposure to biologic therapies, methotrexate and ciclosporin were calculated as cumulative years of exposure by totalling the person years of follow-up for each therapy from initiation to stop or censor (date of cancer diagnosis for cases and their matched controls). Exposure measurement was similar in cases and controls, and was registered before the study outcome. All biologic drugs currently used for psoriasis were grouped because most patients have received several different biologics and, given the long latency (cancer is linked to a drug if the patient was ever exposed to it¹³), it is not possible to link the outcome to any single drug. We used cumulative length of exposure aiming to detect a dose-response effect to provide more power and strengthen the potential causality of the association.

Confounders

Other expected confounders included in the regression models were: cumulative years of exposure to methotrexate and ciclosporin; duration of psoriasis (years from diagnosis to censor); smoking status; prevalence or length of exposure to phototherapy; and the modified Charlson Comorbidity Index (CCI). Unlike the estimate of risk associated with main exposure, these estimates cannot be considered to represent total-effects of these variables, but effects after considering the effect of biologics in cancer¹⁴.

Calculation of lifetime exposure to conventional systemic drugs was calculated by adding the time of exposure while in the cohort and the description of length of exposure that patients gave at entry in the cohort, excluding BADBIR where only prospective exposures were available.

Data on previous exposure to phototherapy had variable accuracy as described in Table 2.

The CCI is a good measure of health resources use and health status. The CCI is robust to modifications as several variants have been used producing similar results¹⁵. CCI acts like propensity scores, and it has been shown in Cox models that adding the individual components to the model produces minimum improvement over the use of CCI.¹⁶ In this study each registry calculated CCI on the available variables, excluding previous cancers: BADBIR and Clalit had data on the 17 variables that make the index, Psocare on 16, and Biobadaderm on 11.

Single registry analyses and combined results

Unit of analysis were patients and the first tumour was considered as outcome. Missing variables were dealt with as described in Table 2. Results were expressed as absolute numbers and percentages (categorical data), mean and standard deviation (normally distributed continuous data), and median and interquartile range for (skewed continuous data). Data were analysed using Stata Statistical Software (StataCorp release 14.2. 2015. College Station, TX: StataCorp LP).

The main outcome was the odds ratio (OR) of cancer associated with cumulative years of exposure to biologic therapies in cases versus controls. Each registry produced univariate analyses (Chi² for categorical and two-sample T-test for continuous variables) to compare main exposure and

confounders between those with and without cancer. Conditional logistic regression was used to perform the multivariable analyses. Each centre produced three models: a model with overall cumulative exposure to biologics (raw effect), one adjusting for lifetime cumulative exposure to methotrexate and ciclosporin, and a final fully-adjusted model including all confounders (Table 1). Using this method had advantages over commonly used time-based methods, as these give more weight to the time between exposure and outcome than to the cumulative level of exposure. However, a cancer that is very close to a short exposure is unlikely to be due to it, but a cancer that takes place long after an intense exposure is more likely to be due to the exposure.

Sensitivity analyses were performed reproducing the same analysis on a population that included SCC among the tumours, and a second with SCC and BCC. The number of SCC did not allow for risk assessment of this tumour type. Pathology reports for skin cancer are not available in the Clalit database, so this group could not run sensitivity analyses.

Meta-analysis of these results using a random-effects model was the main outcome of the study.

RESULTS

Characteristics of participating registries and patients

The characteristics of the studies and patients enrolled in the four participating sub-studies are described in Table 2. The overall study population consisted of 27,376 patients and 58,978 person-years of follow-up. For the main result we had data on 579 cancer cases and 2,671 matched controls. Regarding specific cancer types, we had data for Italy, Spain and UK/ROI, with a total of 41 cases of SCC and 108 cases of BCC.

Before matching, in the overall populations, cancer cases were older, with higher Charlson index, and longer duration of follow-up (Table 3). Multiple tumours by patient were uncommon (Supplementary Table 1). Patients in BADBIR were more likely to have been exposed to psoralen and ultraviolet A therapy (PUVA). There were no significant differences in the length of exposure to biologics between cases and controls. After matching, differences between cases and controls were present the prevalence of previous exposure to psoralen-ultraviolet-A (PUVA) and smoking in UK/ROI, and in the CCI in UK/ROI, Spain and Italy.(Table 3).

Results from multivariable analyses and meta-analysis

Multivariable analysis did not show signs of confounding, as main estimates (Supplementary table 2) did not show changes with progressive adjustment (Figure 1). None of the within registry risk estimates (raw or adjusted) showed a significantly increased risk of cancer per cumulative year of exposure to biologics. Results were homogeneous (I^2 of the fully adjusted model: 34,5%, 3,5% and 0% for the other models) and the pooled adjusted odds ratio of cancer per year of exposure to biologics was 1.02 (95%CI: 0.92-1.13) (Figure 1).

The results in the sensitivity analyses, that included analysis with BCC and SCC, were unmodified and non-significant (Figure 2). We checked in the Biobadaderm dataset that matching on year of enter in the cohort did not lead to relevant changes in the results.

DISCUSSION

Cumulative length of exposure to biologics was not associated with the risk of developing cancers, even after controlling for the effect of age, gender, location, previous exposure to methotrexate, ciclosporin and phototherapy, duration of psoriasis, and comorbidities. Within registry comparisons gave homogeneous results.

This study has advantages, such as being more representative of clinical practice than clinical trials and generalizable to similar settings¹⁷. We have measured risks on the medium-term with several years of median follow-up. BADBIR, Biobadaderm and Psocare are prospective studies cohorts. BADBIR and Biobadaderm are likely to represent clinical practice in UK/ROI and Spain, while Clalit Health Services database and Psocare represent population-based data. Having similar results for all measures of risk in different settings and with different methods reinforces the robustness of our results.

Limitations of this study include that it is observational and uncontrolled confounding could occur¹⁸. As controlling for well-known important confounders did not change our results, it seems unlikely that other minor confounders would have important effects.

Measurement error in some confounders (smoking, previous exposure to immunosuppressive drugs), if non-random, could lead to bias. Against this possibility is that the error should vary among participating registries and estimates are similar.

All biologic drugs may not have comparable associated risks of cancer. With a number of outcomes per study ranging from 52 to 269, we lacked adequate power to detect and compare risk between individual drugs. Furthermore, given the long latency in cancer after exposure and the multiple exposures to different biologics for psoriasis patients it might not be possible to link cancer to single drugs. Differences in risks among biologics remain to be studied.

Another limitation is that we have considered lifetime exposure to biologics without taking into account that different latency periods might act as effect modifiers. Matching on date of entry in the cohorts could partially diminish this issue but could also lead to overmatching. We have checked in Biobadaderm data that this matching did not affect results. As our data describe limited follow-up and latencies, it is still possible than a risk after longer periods of exposure and latencies exists.

Exposure to biologic drugs might not increase the risk of all cancers, but only some like lymphoma or SCC, and merging them all might hide the risk of these few cancers. However, our study is not powered enough to detect increases in risks of lymphoma, SCC or any single type of cancer, and data ownership issues limited further analysis for this study. Further investigation of the types of cancers that develop following exposure to immunosuppressive anti-psoriatic therapies in the studies contributing to this meta-analysis is needed.

These studies are also affected by prescription bias: patients with a higher risk of cancer could be less likely to be prescribed biologics. However, we do not think that this limitation is relevant, as after excluding patients with previous cancer it is unlikely that doctors can predict the risk of cancer in most patients by factors different from those controlled for (age and Charlson).

Merging data from multiple registries increased the statistical power of our study. The most likely estimate in agreement with our data is an unmodified risk of cancer in systemically treated psoriasis patients, linked to the use of biologics for a few years. More conservatively, by considering the upper 95% CI of ORs, our data are compatible with a maximum increased risk of cancer of about 13% per year of therapy. Currently it is unclear as to what the maximum clinically acceptable increase in risk of cancer is in these patients.

A recent systematic review concluded that previous studies do not suggest an increased risk of cancer in patients treated with biologics, except for a possible link between non-melanoma skin cancer (NMSC) and anti-TNF exposure. However, previous results are limited due to the use of historic or general population comparator groups and lack of adjustment for highly relevant confounding factors such as prior phototherapy. Our study uses concurrent controls with psoriasis and adjusts for main confounders. The number of cancers in our data and data ownership limitations did not allow for analysis on any specific tumour to be done.

PSOLAR, an industry promoted study, published results based on half the number of cancer cases than in our study¹⁹. They excluded NMSC from their result and linked cancer to a drug only if patients received it within the year before cancer diagnosis. Their main outcome was an increased risk of cancers in patients exposed to anti-TNF for more than one year, but this result depends on the method used to link drug and outcome. In this study with centres from several continents, pooling all data might lead to confounding, as exposure to therapy and outcome (cancer risk) can show geographic variation. Our study is based on more valid within-country comparisons, includes results of NMSC and aims to describe a dose-effect relationship with all biologic exposure, as we believe that it is not possible to link the outcome to a single drug.

Taken together, data from our registries including nearly 60,000 person-years of observation indicate that cumulative exposure to biologics of psoriasis patients in real-world clinical practice is not associated with an overall higher risk of cancer in the medium-term, after several years of use and latency. Given the heterogeneity of the data sources and methodological limitations, it remains unclear if use of biologics, or only some of them, may be associated with an increased (albeit small) risk of certain cancer subtypes.

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Table 1. Summary of the models produced.

Models	MD (First Model)	MD+SCC (Second Model)	MD+SCC+BCC (Third Model)
Crude: cumulative exposure to biologics (years)	All registries	BADBIR BIOBADADERM Psocare	BADBIR BIOBADADERM Psocare
Adjustment 1: crude + cumulative exposure to methotrexate and ciclosporin (years)	All registries	BADBIR BIOBADADERM Psocare	BADBIR BIOBADADERM Psocare
Adjustment 2: (1) + confounders (CCI; UV exposure; psoriasis disease duration; smoking status)	All registries	BADBIR BIOBADADERM Psocare	BADBIR BIOBADADERM Psocare

Abbreviations:

MD = main dataset; SCC = cutaneous squamous cell carcinoma; BCC = basal cell carcinoma; BADBIR = The British Association of Dermatologists Biologic Interventions Register; Biobadaderm= Spanish Registry of Systemic Therapy in Psoriasis; Psocare= Italian Registry of Systemic Therapy in Psoriasis; CCI = Charlson Comorbidity Index; UV = ultraviolet.

Table 2. Description of the participating sub-studies and characteristics of the patients.

General data: description of the overall cohort				
Registry name	BIOBADADERM	BADBIR	PsoCare	Clalit*
Country	SPAIN	UK & ROI	Italy	Israel
Number of patients included	2456	12314	11490	1116*
Year of start-year of data collection	Oct 2008- Nov 2016	2007-Aug 2016	2005 -2010	2005-Dec 2016
Number of person-years of follow-up	9425,85	30961 for all patients; not censored at cancer diagnosis for included patients	14871,47	3719,67*
Description of missing data and how registries dealt with them	10% (max) missing data in smokers, 5% in some other covariates (comorbidities). Multiple imputation.	Identified controls for each case first; only one matched control had a missing disease onset, smoking set to ever (current/past) and never (never/missing)	Comorbidities<5% (signal detection imputation), smoke and duration <5% (stratified imputation)	4,4% missing data in smoking status, 0,1% missing data in Charlson, Multiple imputation methods.
Exposure to each previous treatment in the cohort (person-years):				
Methotrexate	1809,2	5230,4	1022,7	NA
Ciclosporin	392,0	1795,4	1732,8	NA
Infliximab	554,4	887,4	1375,8	NA
Adalimumab	2069,6	10112,1	453,2	NA
Etanercept	1738,9	3337,3	3431,5	NA
Ustekinumab	1953,5	5817,7	0	NA
Acitretine	797,4	1468,1	857,8	NA
Others: Apremilast, Efalizumab, Secukinumab and others.	111,0	1197,0	1792,8	NA
Phototherapy				
Phototherapy: completeness of registration	Data available on length of exposure to phototherapy before entry in the cohort	Number of patients ever exposed to PUVA (%)	Data available on length of exposure to phototherapy before entry in the cohort, and during follow-up. Only PUVA treated patients were enrolled. UVB-treated patients at	Lifetime exposure

			baseline were not enrolled.	
Number of patients exposed to phototherapy using the above definition	917 (37%)	3153 (26%)	396 (3%)	215 (18%)
Outcomes: number of cancer cases in the different datasets				
Number of first cancer cases (Main dataset)	69 (after excluding 10 cases due to cancer before entry in the cohort)	189 (after excluding 10 cases due to cancer before entry in the cohort)	52 (after excluding 14 cases due to cancer before entry in the cohort)	269
Number of first cancer cases (Main dataset + SCC)	73 (after excluding 10 cases due to cancer before entry in the cohort)	222 (after excluding 31 cases due to cancer before entry in the cohort)	56 (after excluding 14 cases due to cancer before entry in the cohort)	NA
Number of first cancer cases (Main dataset + SCC+BCC)	98 (after excluding 13 cases due to cancer before entry in the cohort)	274 (after excluding 63 cases due to cancer before entry in the cohort)	87 (after excluding 17 cases due to cancer before entry in the cohort)	NA

Abbreviations:

UK = United Kingdom; ROI = Republic of Ireland; MD = main dataset; SCC = cutaneous squamous cell carcinoma; BCC = basal cell carcinoma; BADBIR = The British Association of Dermatologists Biologic Interventions Register; Biobadaderm= Spanish Registry of Systemic Therapy in Psoriasis; Psocare= Italian Registry of Systemic Therapy in Psoriasis; UV = ultraviolet.

*Data in this column do not refer to the whole Clalit database (source population) but to the group of psoriasis patients with cancer and their matched controls. Rates cannot be calculated on these data.

Table 3. Description of the cases and controls in each sub-study, before and after matching.

Registry name	BIOBADADERM			BADBIR			PsoCare			Clalit		
	Cases	Controls	p-value	Cases	Controls	p-value	Cases	Controls	p-value	Cases	Controls	p-value
Results in full registry, including skin cancer (before matching)												
Number of patients	98	2280		274	10117		87	11271		NA	NA	NA
Mean age patients at cancer diagnosis (SD)	62,1 (13,0)	50,2 (14,5)	0,000	56,6 (12,3)	44,7 (13,2)	0,000	60,1 (13,2)	48,5 (14,2)	0,000	NA	NA	NA
Number of female patients (Percentage)	42 (42,9%)	912 (40,0%)	0,527	123 (44,9%)	4161 (41,3%)	0,235	36 (41,4%)	3734 (33,1%)	0,100	NA	NA	NA
Mean duration of exposure to biologics (SD)(years)	2,9 (2,8)	2,6 (2,9)	0,344	1,7 (0,1)	1,6 (1,5)	0,351	0,4 (0,6)	0,5 (0,7)	0,295	NA	NA	NA
Mean duration of exposure to methotrexate (SD) (years)	0,8 (1,6)	0,7 (1,4)	0,651	1,3 (1,5)	1,0 (1,1)	0,007	0,1 (0,3)	0,1 (0,3)	0,608	NA	NA	NA
Mean duration of exposure to ciclosporin (SD) (years)	0,2 (0,5)	0,2 (0,5)	0,892	0,6 (0,8)	0,6 (0,8)	0,830	0,1 (0,2)	0,2 (0,4)	0,097	NA	NA	NA
Mean duration of exposure to phototherapy (SD) (years)	0,3 (0,7)	0,3 (0,5)	0,348				0,01 (0,02)	0,02 (0,15)	0,386	NA	NA	NA
Patients ever exposed to PUVA (% of group)				119 (43,4%)	2959 (30,0%)	0,000				NA	NA	NA
Mean modified Charlson index (SD)	0,8 (1,3)	0,4 (0,9)	0,000	0,6 (0,8)	0,4 (0,6)	0,000	0,5 (1,2)	0,3 (0,7)	0,004	NA	NA	NA
Number of ever smokers (percentage)	44 (54,3%)	921 (50,7%)	0,529	159 (58,0%)	5714 (57,9%)	0,970	58 (66,7%)	6766 (60,0%)	0,208	NA	NA	NA
Mean duration of psoriasis at baseline (SD) (years)	26,5 (14,0)	22,0 (13,1)	0,001	26,8 (14,7)	20,9 (12,6)	0,000	23,1 (14,4)	17,1 (12,4)	0,000	NA	NA	NA
Results in full registry, including skin cancer (after matching on year of birth, gender, geographic area, and registration year)												
Number of patients	98	392		274	1089		87	343		269	847	
Mean age at cancer diagnosis (SD)	62,1 (13,0)	61,1 (13,0)	0,515	59,0 (12,2)	59,1 (12,1)	0,899	60,1 (13,2)	59,5 (12,9)	0,724	64,9 (13,6)	65,3 (12,8)	0,672
Number of females (percentage)	42 (42,9%)	166 (42,4%)	0,927	123 (44,9%)	486 (44,6%)	0,938	36 (41,4%)	139 (40,5%)	0,885	139 (51,7%)	432 (51,0%)	0,848
Mean duration of exposure to biologics (SD)	2,9 (2,8)	4,0 (3,2)	0,002	1,5 (1,7)	1,5 (1,6)	0,867	0,4 (0,6)	0,5 (0,7)	0,338	0,2 (0,8)	0,1 (0,5)	0,345

(years)												
Mean duration of exposure to methotrexate (SD) (years)	0,8 (1,6)	1,0 (1,7)	0,398	0,5 (1,2)	0,7 (1,3)	0,149	0,1 (0,3)	0,1 (0,4)	0,196	1,3 (1,6)	1,2 (1,6)	0,449
Mean duration of exposure to ciclosporin (SD) (years)	0,2 (0,5)	0,1 (0,4)	0,614	0,2 (0,6)	0,2 (0,5)	0,860	0,1 (0,2)	0,1 (0,2)	0,434	0,1 (0,7)	0,03 (0,3)	0,09
Mean duration of exposure to phototherapy (years)	0,3 (0,7)	0,3 (0,7)	0,608				0,01 (0,2)	0,01 (0,1)	0,777	0,2 (0,5)	0,2 (0,6)	0,63
Patients ever exposed to PUVA (% of group)				119 (43,4%)	366 (34,9%)	0,010						
Mean modified Charlson index (SD)	0,8 (1,3)	0,5 (1,0)	0,018	0,5 (0,8)	0,4 (0,7)	0,090	0,5 (1,2)	0,4 (0,8)	0,345	1,2 (1,4)	1,3 (1,5)	0,5
Number of ever smokers (Percentage)	44 (54,3%)	174 (51,0%)	0,594	159 (58,0%)	552 (50,7%)	0,030	58 (66,7%)	212 (61,8%)	0,402	128 (50,6%)	376 (46,2%)	0,57
Mean duration of psoriasis at diagnosis of cancer in the matched case(SD) (years)	22,8 (14,3)	25,6 (15,2)	0,104	29,2 (14,7)	28,1 (14,5)	0,410	23,1 (14,4)	19,8 (14,0)	0,055	10,5 (10,3)	9,8 (9,4)	0,30

Abbreviations:

MD = main dataset; SCC = cutaneous squamous cell carcinoma; BCC = basal cell carcinoma; BADBIR = The British Association of Dermatologists Biologic Interventions Register; Biobadaderm= Spanish Registry of Systemic Therapy in Psoriasis; Psocare= Italian Registry of Systemic Therapy in Psoriasis; CCI = Charlson Comorbidity Index; UV = ultraviolet; SD=Standard deviation.

FIGURE LEGENDS

Figure 1. Forest plot describing random effects meta-analysis of the estimates of the OR of cancer (skin cancer excluded) per year of cumulative lifetime exposure to biologics. Ad1 (after adjusting for lifetime exposure to methotrexate and ciclosporin), Adj2 (after adjusting for lifetime exposure to methotrexate and ciclosporin, duration of psoriasis, smoking, length of exposure to phototherapy and modified Charlson index). Patients were matched on date of birth, gender, geographic area and year of entry in the cohort.

Figure 2. Results of sensitivity analysis in the different participating studies. Estimates of the OR of cancer per year of cumulative lifetime exposure to biologics. MD (main dataset), SCC (squamous cell carcinoma), BCC (basal cell carcinoma), Ad1 (after adjusting for lifetime exposure to methotrexate and ciclosporin) , Adj2 (after adjusting for lifetime exposure to methotrexate and ciclosporin, duration of psoriasis, smoking, length of exposure to phototherapy and modified Charlson index). Patients were matched on date of birth, gender and geographic area and year of entry in the cohort. Pathology reports for skin cancer are not available in the Clalit database, so this group could not run sensitivity analyses.