



Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry

Paula Dávila-Seijo^{1,15}, Esteban Dauden², M.A. Descalzo¹, Gregorio Carretero³, José-Manuel Carrascosa⁴, Francisco Vanaclocha⁵, Francisco-José Gómez-García⁶, Pablo De la Cueva-Dobao⁷, Enrique Herrera-Ceballos⁸, Isabel Belinchón⁹, José-Luis López-Estebanz¹⁰, Merce Alsina¹¹, José-Luis Sánchez-Carazo¹², Marta Ferrán¹³, Rosa Torrado³, Carlos Ferrandiz⁴, Raquel Rivera⁵, Mar Llamas², Rafael Jiménez-Puya⁶ and Ignacio García-Doval^{1,14} and the BIOBADADERM Study Group

Information regarding the safety of biological drugs prescribed to psoriasis patients on daily and long-term bases is insufficient. We used data from the BIOBADADERM registry (Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases) to generate crude rates of infection during therapy with systemic drugs, including biological drugs (infliximab, etanercept, adalimumab, and ustekinumab) and nonbiological drugs (acitretin, cyclosporine, and methotrexate). We also calculated unadjusted and adjusted risk ratios (RRs) (with propensity score adjustment) of infection, serious infections, and recurrent infections of systemic therapies compared with methotrexate, using Poisson regression. Our study included records of 2,153 patients (7,867.5 person-years). The adjusted RR of overall infection was significantly increased in the groups treated with adalimumab with methotrexate (adjusted RR = 2.13, 95% confidence interval [CI] = 1.2–3.7), infliximab (adjusted RR = 1.71, 95% CI = 1.1–2.65), cyclosporine (adjusted RR = 1.58, 95% CI = 1.17–2.15), ustekinumab with methotrexate (adjusted RR = 1.56, 95% CI = 1.08–2.25), and etanercept (adjusted RR = 1.34, 95% CI: 1.02–1.76) compared with methotrexate alone. Cyclosporine had a significant risk of serious infection (adjusted RR = 3.12, 95% CI = 1.1–8.8), followed by adalimumab combined with methotrexate (adjusted RR = 3.28, 95% CI = 0.8–13.5). Adalimumab in combination with methotrexate had the highest risk of infection recurrence (adjusted RR = 4.33, 95% CI = 2.27–8.24).

Journal of Investigative Dermatology (2017) **137**, 313–321; doi:10.1016/j.jid.2016.08.034

INTRODUCTION

Psoriasis is a chronic skin disease that affects between 0.91% and 8.5% of the population (Ferrandiz et al., 2014; Parisi et al., 2013) across the world. Of those affected, approximately 10% suffer from severe forms of psoriasis. Traditionally, therapeutic options for treating moderate to severe psoriasis have been limited. Three of the so-called “nonbiological systemic therapies” were the most commonly used systemic drugs worldwide: acitretin, cyclosporine, and methotrexate. Biological drugs have been authorized

for use in moderate and severe forms of psoriasis: tumor necrosis factor (TNF) antagonists (infliximab, etanercept, and adalimumab) and one IL-12/23 antagonist (ustekinumab).

Clinical trials of these drugs have shown high rates of serious infections in rheumatoid arthritis, but these have not been confirmed in all trials because of the lack of statistical power to demonstrate differences from placebo (Gordon et al., 2012; Reich et al., 2012; Salliot et al., 2007; Salmon-Ceron et al., 2011; Schmitt et al., 2014;

¹Research Unit, Fundación Academia Española de Dermatología y Venereología, Madrid, Spain; ²Dermatology Department, Hospital Universitario La Princesa, Madrid, Spain; ³Dermatology Department, Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria, Spain; ⁴Dermatology Department, Hospital Universitario Germans Trias i Pujol, Badalona, Spain; ⁵Dermatology Department, Hospital Universitario 12 de Octubre, Madrid, Spain; ⁶Dermatology Department, Hospital Universitario Reina Sofía, Córdoba, Spain; ⁷Dermatology Department, Hospital Infanta Leonor, Madrid, Spain; ⁸Dermatology Department, Hospital Universitario Virgen de la Victoria, Málaga, Spain; ⁹Dermatology Department, Hospital General Universitario de Alicante, Departamento de Medicina Clínica, Universidad Miguel Hernández, ISABIAL–FISABIO, Alicante, Spain; ¹⁰Dermatology Department, Hospital Universitario Fundación Alcorcón, Madrid, Spain; ¹¹Dermatology Department, Hospital Clinic de Barcelona, Barcelona, Spain;

¹²Dermatology Department, Hospital General Universitario de Valencia, Valencia, Spain; ¹³Dermatology Department, Hospital del Mar, Parc de Salut Mar, Barcelona, Spain; ¹⁴Dermatology Department, Complejo Hospitalario Universitario de Vigo, Vigo, Spain; and ¹⁵Dermatology and Venereology Department, Umeå University Hospital, Umeå, Sweden

Correspondence: Paula Dávila-Seijo, Research Unit, Fundación Academia Española de Dermatología, Ferraz 100, 1^o izda, Madrid. E-mail: pauladavilaseijo@gmail.com

Abbreviations: BIOBADADERM, Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases; CI, confidence interval; PASI, Psoriasis Area Severity Index; RR, risk ratio; TNF, tumor necrosis factor

Received 6 May 2016; revised 29 July 2016; accepted 31 August 2016; accepted manuscript published online 25 September 2016; corrected proof published online 15 November 2016

Soderlin et al., 2005; Suwannalai et al., 2009; Trautmann, 2012; Trotta and Valentini, 2005; Wood et al., 2003).

Safety claims of biological drugs for other indications cannot be extrapolated uncritically to psoriasis or dermatological patients (Andersen and Jess, 2014; Atzeni et al., 2012; Galloway et al., 2011; Garcia-Doval et al., 2016; Sakai et al., 2012; van Dartel et al., 2013). Comorbidities of each of the underlying conditions often vary and can be expected to alter the safety profile of biological drugs (Wakkee et al., 2011).

A recent systematic review and meta-analysis stated that there was still not enough evidence about the risk of serious infections from biological drugs in psoriasis patients in long-term and daily use and that further observational studies were needed (Yiu et al., 2016).

OBJECTIVES

Our objectives were as follows: (i) to describe the infections that occurred in patients who received biological drugs and those who received nonbiological systemic drugs in the Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases (BIOBADADERM) registry and (ii) to compare the risk of infections, risk of serious infections, and risk of infection recurrence for each of the different biological and nonbiological drugs with those for methotrexate and to evaluate changes in the rate of overall infection during the study period.

RESULTS

At the end of the follow-up period, 2,153 patients were included for analysis. Of them, 1,074 were exposed to biologics and 1,079 to nonbiological therapies (some patients were exposed to both during follow-up), with 7,867.5 person-years at the end of the follow-up period (see [Supplementary Table S1](#) online). Only 0.3% of patients declined to participate. Losses to follow-up numbered 257 (11.9%).

[Tables 1](#) and [2](#) show the patients' baseline characteristics and their drug regimens. Overall, the patient group receiving biologics had a higher proportion of men and higher prevalence of the plaque type of psoriasis and psoriatic arthritis. The Psoriasis Area Severity Index (PASI) score when starting therapy, duration of disease at the beginning of treatment, and the number of previous treatments were also higher in patients ever receiving biologics.

Risk of overall infections

Infliximab and etanercept in monotherapy showed a significant higher risk of overall infection compared with methotrexate in the adjusted analysis ([Table 3](#), and see [Supplementary Figure S1](#) and [Supplementary Table S2](#) online). Among the nonbiological therapies, acitretin showed the lowest infection risk compared with methotrexate (crude risk ratio [RR] = 0.6, 95% confidence interval [CI] = 0.42–0.86); after multivariable and propensity score adjustments, this decrease in risk was still significant (adjusted RR = 0.6, 95% CI = 0.44–0.83). Cyclosporine showed a 58% higher risk of overall infection than methotrexate (adjusted RR = 1.58, 95% CI = 1.17–2.15).

Risk of serious infections

The number of serious infections ([Table 4](#)) was low among all the treatments, with the highest rate in the combined

adalimumab and methotrexate group (adjusted incidence rate = 23.3, 95% CI = 12.9–42), followed by the cyclosporine group (adjusted incidence rate = 20, 95% CI = 8.3–47.9) and the infliximab group (adjusted incidence rate = 18.9, 95% CI = 7.9–45.5). Because of the small number of serious infections, it was not possible to obtain significant RRs compared with methotrexate and the CIs were wide, especially after adjustment. The combinations of infliximab and adalimumab with methotrexate had the highest risk of serious infections compared with methotrexate alone, although they did not reach significance. Cyclosporine had a significant higher risk of serious infections than methotrexate in both crude and adjusted analysis (adjusted RR = 3.12, 95% CI = 1.11–8.77).

Risk of recurrent infections

The crude rate (per 1,000 person-years) of recurrent infections varied among the therapy groups, from the highest rate of 80.4 (95% CI = 58.5–110.4) in the combined group of adalimumab and methotrexate to the lowest rate of 13.3 (95% CI = 6.3–27.9) in the acitretin group. In terms of risk of recurrent infections ([Table 5](#)), the combined adalimumab and methotrexate group had the higher risk (adjusted RR = 4.33, 95% CI = 2.27–8.24), followed by infliximab (adjusted RR = 1.98, 95% CI = 1–3.94). Acitretin had a significantly lower risk of recurrent infections compared with methotrexate (adjusted RR = 0.45, 95% CI = 0.23–0.87).

Changes in the rate of infections over the length of the study

Our study found no significant changes over time (see [Supplementary Figure S2](#) online) in the incident rate (per 1,000 person-years) of infections compared with the incident rate in patients taking methotrexate, except with ustekinumab, which showed a significant tendency toward decreasing the rate of overall infections over time.

DISCUSSION

To our knowledge, this is the first multicenter, longitudinal, disease-based analysis of risk of overall infections, serious infections, and infection recurrence among moderate to severe psoriasis patients taking both classic and biological systemic drugs. We found a slight, significant adjusted increase in the risk of overall infection between the TNF-antagonist drugs and methotrexate. Acitretin had a 40% lower raw risk of infection than methotrexate, and this reduction remained significant in the adjusted analysis.

The rates of serious infections we found are comparable with those recently reported in the Psoriasis Longitudinal Assessment and Registry study (Kalb et al., 2015), a large multicenter, prospective psoriasis study, which includes patients from many countries, although patients from North America are overrepresented. Similar to the results of our study, the Psoriasis Longitudinal Assessment and Registry study found that infliximab was the drug with the highest rate of serious infections (24.9 per 1,000 person-years). Adalimumab was also the drug with the second-highest rate, but our finding was not as high as their reported rate of 19.7 per 1,000 person-years. Our study found that etanercept had the smallest unadjusted rate of all drugs (1.6 per 1,000 person-years), whereas the Psoriasis Longitudinal Assessment and Registry study found a rate of 14.7 per 1,000 persons-years for etanercept.

Table 1. Baseline characteristics of patients in the study¹

	Etanercept	Infliximab	Adalimumab	Ustekinumab	Acitretin	Cyclosporine	Methotrexate
Patients, n (%)	635 (100)	184 (100)	683 (100)	560 (100)	467 (100)	472 (100)	880 (100)
Cycles, n (% of all treatments)	885 (17.8)	207 (4.2)	898 (18.1)	663 (13.3)	590 (11.9)	574 (11.6)	1154 (23.2)
Cycles that represent first use of the drug, n (% of all cycles)	399 (18.5)	86 (4.0)	3334 (15.5)	188 (8.4)	291 (13.5)	292 (13.6)	567 (26.3)
Women, n (%)	270 (42.5)	64 (34.8)	255 (37.3)	235 (42.0)	153 (32.8)	223 (47.3)	388 (44.1)
Age, years (SD)	50.8 (14.3)	49.8 (12.1)	48.9 (12.6)	49.6 (13.8)	56.3 (15.3)	45.5 (13.9)	50.1 (14.8)
Duration of disease at start of treatment in years, median (p25–p75)	9 (15.7–25.6)	10.2 (18–26.8)	9.3 (16.8–26.2)	10.1 (17.8–27.7)	5.5 (12.6–26.4)	6.1 (12.8–22.5)	5.4 (12.8–23.5)
PASI score, median (p25–p75)	7 (10.8–16)	7.9 (15.8–22.6)	7.3 (12–17.4)	8.7 (12–18)	4 (7.2–11.5)	7.1 (11.2–16.8)	4.1 (7.4–11.3)
Diagnosis at registration in cohort, n (% of total)							
Plaque psoriasis	613 (96.5)	166 (90.2)	644 (94.3)	534 (95.4)	401 (85.9)	426 (90.3)	821 (93.3)
Other forms ²	60 (9.5)	25 (13.6)	67 (9.8)	55 (9.8)	85 (18.2)	70 (14.8)	99 (11.3)
Psoriatic arthritis	116 (18.3)	40 (21.8)	138 (20.2)	80 (14.3)	30 (6.4)	34 (7.2)	101 (11.5)
Comorbidities, n (% of total patients)							
Ischemic cardiopathy	17 (2.7)	2 (1.1)	11 (1.6)	9 (1.6)	20 (4.3)	6 (1.3)	29 (3.3)
Arterial hypertension	127 (20)	35 (19.2)	142 (20.8)	110 (19.6)	143 (30.6)	52 (11.0)	203 (23.1)
Diabetes	70 (11.0)	26 (14.3)	78 (11.4)	61 (10.9)	78 (16.7)	34 (7.2)	90 (10.2)
Hypercholesterolemia	157 (24.7)	46 (25)	175 (25.6)	140 (25)	144 (30.8)	89 (18.9)	249 (28.3)
Cancer in the past 5 years ³	10 (1.6)	5 (2.7)	12 (1.8)	11 (2.0)	46 (9.9)	4 (0.9)	35 (4.0)
Chronic hepatopathy	46 (7.2)	14 (7.6)	34 (5.0)	27 (4.8)	24 (5.1)	22 (4.7)	17 (1.9)
Chronic renal failure	12 (1.9)	2 (1.1)	3 (0.45)	6 (1)	6 (1.3)	0 (0)	7 (0.8)
COPD	13 (2.1)	2 (1.1)	12 (1.8)	12 (2.1)	18 (3.9)	8 (1.7)	11 (1.3)
Hepatitis B	33 (5.2)	7 (3.8)	21 (3.0)	16 (2.9)	25 (5.4)	12 (2.6)	29 (3.3)
Hepatitis C	28 (4.4)	6 (3.3)	8 (1.2)	8 (1.4)	16 (3.4)	9 (1.9)	9 (1.0)
HIV	8 (1.3)	0 (0)	4 (0.6)	8 (1.4)	7 (1.5)	5 (1.1)	7 (0.8)
Cycles with simultaneous administration of other systemic drug (n, % of all cycles)							
Methotrexate	95 (10.7)	75 (36.2)	142 (15.8)	84 (12.7)	13 (2.3)	8 (1.4)	⁴
Acitretin	32 (3.6)	9 (4.3)	14 (1.6)	25 (3.8)	⁴	6 (1.0)	15 (1.3)
Cyclosporine	34 (3.8)	9 (4.3)	52 (5.8)	27 (4.1)	12 (2.2)	⁴	5 (0.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; p25–p75, 25th percentile to 75th percentile; PASI, Psoriasis Area Severity Index (at the beginning of each treatment); SD, standard deviation.

¹Columns represent the different drugs prescribed to participants. The total number of patients was 2,153.

²Other forms of psoriasis: erythrodermic psoriasis, generalized pustular psoriasis, palmoplantar pustulosis, annular pustular psoriasis, and acrodermatitis continua of Hallopeau.

³Excluding nonmelanoma skin cancer.

⁴Not applicable.

Table 2. Baseline characteristics of patients who received combined therapy of a biological drug and methotrexate¹

Characteristic	Etanercept	Infliximab	Adalimumab	Ustekinumab
	In Combination with Methotrexate			
Number of patients, n (%)	88 (100)	74 (100)	130 (100)	84 (100)
Women, n (%)	42 (47.7)	22 (29.7)	54 (41.5)	28 (33.3)
Age, years (SD)	50.5 (13.7)	49.9 (11.5)	48.2 (10.4)	49.6 (11.7)
Duration of disease at start of treatment, median years (p25–p75)	17.4 (10.9–2)	18.7 (10.7–30)	18.1 (10.5–27.3)	18.1 (11.1–26.3)
PASI, median (p25–p75)	8.4 (5.4–13.2)	15 (7.2–22.5)	11.4 (5.1–16)	12 (8–18)
Diagnosis at registration in cohort, n (% of total)				
Plaque psoriasis	84 (95.5)	66 (89.2)	121 (93.1)	81 (96.4)
Other forms	7 (8)	9 (12.2)	8 (6.2)	5 (6)
Psoriatic arthritis ²	25 (28.4)	16 (21.6)	37 (28.5)	24 (28.6)
Comorbidities, n (% of total patients)				
Ischemic cardiopathy	0 (0)	1 (1.4)	3 (2.3)	2 (2.4)
Arterial hypertension	14 (15.9)	19 (25.7)	36 (27.7)	23 (27.4)
Diabetes	5 (5.7)	13 (17.6)	14 (10.8)	9 (10.7)
Hypercholesterolemia	20 (22.7)	22 (29.7)	33 (25.4)	27 (32.1)
Cancer in the past 5 years ³	2 (2.3)	1 (1.4)	2 (1.5)	2 (2.4)
Chronic hepatopathy	1 (1.1)	3 (4.1)	1 (0.8)	2 (2.4)
Chronic renal failure	0 (0)	2 (2.7)	0 (0)	0 (0)
COPD	1 (1.1)	0 (0)	1 (0.8)	2 (2.4)
Hepatitis B	2 (2.3)	5 (6.8)	3 (2.3)	4 (4.8)
Hepatitis C	1 (1.1)	2 (2.7)	0 (0)	0 (0)
HIV	0 (0)	0 (0)	2 (1.5)	1 (1.2)

Abbreviations: COPD, chronic obstructive pulmonary disease; p25–p75, 25th percentile to 75th percentile; PASI, Psoriasis Area Severity Index; SD, standard deviation.

¹Columns list the drugs taken with methotrexate. Total number of patients was 2,153.

²Other forms of psoriasis: erythrodermic psoriasis, generalized pustular psoriasis, palmoplantar pustulosis, annular pustular psoriasis, and acrodermatitis continua of Hallopeau.

³Excluding nonmelanoma skin cancer.

The RR between different drugs compared with a reference drug was not calculated in the Psoriasis Longitudinal Assessment and Registry study, the rate of cyclosporine and acitretin is reported together, and those patients who were treated with a combination of one biological drug and methotrexate are not analyzed specifically.

Risk of serious infection in other diseases

Not much data are available about infection risk and serious infection risk in psoriasis patients under systemic therapy (Yiu et al., 2016). Most post-commercialization long-term studies and registries involve rheumatoid arthritis patients treated with TNF

Table 3. Infection crude rates (per 1,000 person-years) and crude and adjusted incidence RR of infection compared with methotrexate¹

	Person-time	Failures	Rate (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Etanercept	1,228.6	183	148.9 (128.9–172.2)	1.23 (0.94–1.62)	1.34 (1.02–1.76) ^{2,5}
Infliximab	264.2	56	211.9 (163.1–275.4)	1.63 (1.09–2.44) ⁵	1.71 (1.10–2.65) ⁵
Adalimumab	1,329.7	195	146.6 (127.4–168.7)	1.22 (0.89–1.66)	1.27 (0.92–1.75) ³
Ustekinumab	1,194.0	138	115.6 (97.8–136.6)	0.91 (0.62–1.34)	0.93 (0.64–1.36) ⁴
Methotrexate	1,149.4	130	113.1 (95.2–134.3)	1.00	1.00
Cyclosporine	250.6	43	171.6 (127.3–231.4)	1.57 (1.17–2.12) ⁶	1.58 (1.17–2.15) ⁶
Acitretin	526.8	34	64.5 (46.1–90.3)	0.6 (0.42–0.86) ⁶	0.6 (0.44–0.83) ⁶
Etanercept combined with methotrexate	284.7	31	105.7 (73.0–153.1)	1 (0.50–1.99)	1.02 (0.52–1.99) ²
Infliximab combined with methotrexate	225.6	25	104 (68.5–158.0)	1.12 (0.59–2.11)	1.23 (0.68–2.23)
Adalimumab combined with methotrexate	472.9	91	195.6 (157.7–242.6)	2.04 (1.28–3.26) ⁶	2.13 (1.23–3.67) ^{3,6}
Ustekinumab combined with methotrexate	340.2	56	173.2 (132.0–227.3)	1.39 (0.96–2.02)	1.56 (1.08–2.25) ^{4,5}

Abbreviations: CI, confidence interval; RR, risk ratio.

¹Adjusted for age, sex, and propensity score of each drug compared with methotrexate.

²Additional adjustment for baseline Psoriasis Area Severity Index and psoriasis arthritis.

³Additional adjustment for disease duration.

⁴Additional adjustment for diabetes and history of tuberculosis.

⁵P < 0.05.

⁶P < 0.01.

Table 4. Serious and deadly infection crude rates (per 1,000 person-years) and crude and adjusted¹ incidence RR of serious and deadly infections compared with methotrexate

	Person-Time	Failures	Rate (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Etanercept	1,228.6	2	1.6 (0.4–6.5)	0.17 (0.03–0.91) ⁵	0.24 (0.04–1.29) ²
Infliximab	264.2	5	18.9 (7.9–45.5)	1.27 (0.49–3.31)	2.52 (0.83–7.69)
Adalimumab	1,329.7	13	9.8 (5.7–16.8)	0.92 (0.46–1.84)	1.29 (0.72–2.32) ³
Ustekinumab	1,194.0	7	5.9 (2.8–12.3)	0.59 (0.12–2.87)	0.75 (0.18–3.13) ⁴
Methotrexate	1,149.4	11	9.6 (5.3–17.3)	1	1
Cyclosporine	250.6	5	20 (8.3–47.9)	2.21 (1.02–4.81) ⁵	3.12 (1.11–8.77) ⁵
Acitretin	526.8	4	7.6 (2.8–20.2)	0.8 (0.33–1.91)	0.82 (0.35–1.92)
Etanercept combined with methotrexate	284.7	2	7 (1.8–28.1)	0.37 (0.11–1.3)	0.56 (0.15–2.1)
Infliximab combined with methotrexate	225.6	2	8.9 (2.2–35.4)	2.11 (0.64–6.95)	3.4 (0.76–15.21)
Adalimumab combined with methotrexate	472.9	11	23.3 (12.9–42)	2.5 (0.7–8.89)	3.28 (0.8–13.46) ³
Ustekinumab combined with methotrexate	340.2	3	8.8 (2.8–27.3)	1.05 (0.24–4.52)	1.63 (0.43–6.13) ⁴

Abbreviations: CI, confidence interval; RR, risk ratio.

¹Adjusted for age, sex, and propensity score of each drug compared with methotrexate.

²Additional adjustment for baseline Psoriasis Area Severity Index and psoriasis arthritis.

³Additional adjustment for disease duration.

⁴Additional adjustment for diabetes and history of tuberculosis.

⁵ $P < 0.05$.

antagonists compared with methotrexate (Garcia-Doval et al., 2016).

Compared with other systemic diseases in which biologics are also used, our study found that psoriasis patients treated with TNF-antagonist drugs (etanercept, infliximab, and adalimumab) had a lower rate of serious infections compared with rheumatoid arthritis patients treated with TNF-antagonist drugs. Data from the British Society for Rheumatology Biologics Register, a database for a large national prospective study that analyzed data from 15,395 patients (11,798 in the TNF antagonist cohort and 3,598 in the nonbiologics cohort) with a median follow-up duration of 3.9 years, showed an unadjusted incidence rate of 38 per 1,000 person-years (95% CI = 35–42) in the group treated with etanercept, an incidence rate of 46 per 1,000 person-years (95% CI = 42–50) in the

group treated with infliximab, and an incidence rate of 43 per 1,000 person-years (95% CI = 39–47) in the group treated with adalimumab. Similar results were found in other prospective cohort studies (Atzeni et al., 2012; Sakai et al., 2012; van Dartel et al., 2013). This reinforces the idea that psoriasis and rheumatoid arthritis cannot be compared, because of their different underlying immunologic alterations and the resulting treatment-specific comorbidities.

Infection recurrence

The raw rate of recurrent infections in the same patient appeared to be higher among patients treated with biologics compared with those treated with methotrexate, and it was lower among patients who were treated with cyclosporine or acitretin. This can be due, especially when time at risk is

Table 5. Recurrent infections crude rates (per 1,000 person-years) and crude and adjusted¹ incidence risk ratio of recurrent infections compared to methotrexate

	Person-Time	Failures	Rate (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Etanercept	1,228.6	70	57 (45.1–72)	1.18 (0.82–1.71)	1.4 (0.93–2.1) ²
Infliximab	264.2	21	79.5 (51.8–121.9)	1.81 (0.86–3.82)	1.98 (1–3.94)
Adalimumab	1,329.7	66	49.6 (39–63.2)	1.03 (0.7–1.53)	1.06 (0.67–1.67) ³
Ustekinumab	1,194.0	45	37.7 (28.1–50.5)	0.77 (0.36–1.61)	0.8 (0.37–1.75) ⁴
Methotrexate	1,149.4	39	33.9 (24.8–46.4)	1	1
Cyclosporine	250.6	5	20 (8.3–47.9)	0.78 (0.43–1.43)	0.63 (0.3–1.31)
Acitretin	526.8	7	13.3 (6.3–27.9)	0.43 (0.23–0.8) ⁵	0.45 (0.23–0.87) ⁵
Etanercept combined with methotrexate	284.7	8	28.1 (14.1–56.2)	0.86 (0.37–2)	0.75 (0.37–1.49) ²
Infliximab combined with methotrexate	225.6	3	13.3 (4.3–41.2)	0.61 (0.17–2.21)	0.66 (0.18–2.44)
Adalimumab combined with methotrexate	472.9	38	80.4 (58.5–110.4)	3.83 (2.47–5.95) ⁶	4.33 (2.27–8.24) ^{3,6}
Ustekinumab combined with methotrexate	340.2	25	73.5 (49.7–108.8)	1.95 (0.49–7.71)	2.18 (0.63–7.48) ⁴

Abbreviations: CI, confidence interval; RR, risk ratio.

¹Adjusted for age, sex, and propensity score of each drug compared with methotrexate.

²Additional adjustment for baseline psoriasis area severity index (PASI) and psoriasis arthritis.

³Additional adjustment for disease duration.

⁴Additional adjustment for diabetes and history of tuberculosis.

⁵ $P < 0.05$.

⁶ $P < 0.01$.

evaluated, to the fact that methotrexate and all classic drugs for psoriasis are usually administered in cycles, and treatment ceases when patients improve because of concerns regarding potential organ damage from long-term use. In particular, the liver is at risk from methotrexate treatment, and the kidneys are at risk from cyclosporine treatment. If a drug is not used continuously, which is the present standard of psoriasis therapy with biological drugs, a patient may not be at prolonged risk of recurrent infections. However, infliximab showed the highest rate of recurrent infections of all biologics, despite having the smallest time at risk. Infliximab also had the highest relative risk of recurrent infection compared with methotrexate of any biologics in both the unadjusted and adjusted analysis. Another factor that could bias this analysis is a depletion of susceptible bias: patients with previous infection could be offered alternative therapies.

Combination therapy

Our study also analyzed the risk of infection among patients undergoing combination therapy of a biological drug and methotrexate. This combination is not uncommon in clinical practice, especially for optimizing efficacy in patients who receive treatment with biologics and who do not reach the desired level of improvement. To date, there are not enough data available about the risk of infection in psoriasis patients treated with a combination of one of the biologics and methotrexate (Armstrong et al., 2015; Yiu et al., 2016). On the basis of mostly long-term data from psoriatic arthritis and rheumatoid arthritis (Breedveld et al., 2006; Greenberg et al., 2010), the combination of adalimumab with methotrexate appears as a suggested option in the latest guidelines (Cather and Crowley, 2014; Nast et al., 2015). A recent report from a 500,000–person-year study in Israel found that the combination of biologics with methotrexate was significantly associated with an increased incidence of herpes zoster (Shalom et al., 2015).

Our study shows a tendency toward increasing rate and relative risk of serious infections for all biologics in combination with methotrexate, compared with the same biologic in monotherapy, despite having a much smaller person/time-at-risk cohort in the combination therapy groups. If this finding is confirmed in other studies, it could have important consequences for clinical practice.

Changes in infection risk over time

The last objective of our study was to evaluate the evolution in time of the rate of infection among patients taking different drugs. We found that the incidence rate of overall infection in all the systemic treatment groups did not change significantly over time in any of the treatments. This contrasts with the reported risk of infections among patients with rheumatoid arthritis treated with TNF-antagonist drugs (etanercept, infliximab, and adalimumab), which appeared to be higher during the first year of treatment and then became nearly constant (Sakai et al., 2012; van Dartel et al., 2013). In our study, only ustekinumab showed a significant trend for a reduction in the overall infection risk over time, and doubt regarding a constant basal rate arose only in the last period of follow-up; this change may be due to the lower sample size during this period.

Limitations

Our study has some limitations. First, it is observational and may suffer from selection bias in the treatments for each patient. Drug allocation was not randomized but was a reflection of common use, leading to groups that were not comparably similar at baseline and possibly confounding by indication. To decrease this potential bias, we adjusted for the propensity score of each drug in the multivariable analysis. In our study, patients who received biologics at any time skewed toward a higher proportion of women and a higher prevalence of plaque-type psoriasis and psoriatic arthritis, a higher PASI score at the start of therapy, longer duration of disease at commencement of treatment, and number of previous treatments. With the propensity score technique, we could remove the indication bias from the non-randomization of patients from the baseline covariates: patients in the comparison groups (treatment of interest group and control) who have similar propensity scores will have nearly the same distribution in the baseline covariates. We did this adjustment as an extra step to control for potential confounders originating from the differences in the baseline covariates distribution; these confounders can emerge from subjectively favoring one treatment over another because the patients have some specific baseline characteristic. Use of this methodology is an important strength of our study compared with previous studies of infection in psoriasis. There can be, however, residual confounding due to non-collected variables, such as inflammatory bowel disease.

Information bias in reporting of adverse events by physicians or patients is also possible. To avoid it, we used standardized definitions of adverse events that should be reported, frequent training of data collectors, and data monitoring. We also established a threshold for including adverse events in the registry (those that led to changes in therapy or caused an unexpected visit to the doctor).

The prescribed doses were not collected. This could mean some error in the measurement of exposure, possibly influencing the results.

Strengths

One of the strengths of our study is that the studied population was highly representative of psoriasis patients in clinical practice. Another is the quality of the data in the BIOBADADERM registry. Our study analyzed data from a large number of patients from different hospitals in Spain and included patients who were not represented in clinical trials. In addition, and this is one of the study's strengths relative to other published studies of infection in psoriasis, we included data on classic drugs and took into account simultaneous use of biologics and classic drugs. We also differentiated between patients who were treated with two immunosuppressive treatments in combination therapy (biological drug and methotrexate) from those treated with only one drug. This is important because the addition of methotrexate could potentially increase the risk of infection.

CONCLUSIONS

In terms of infection prevention, only acitretin had a significant lower adjusted risk than methotrexate, and methotrexate can be considered a reference for safety in terms of

infections. The adjusted RR of overall infections was significantly increased in the groups treated with adalimumab with methotrexate, infliximab, cyclosporine, and ustekinumab combined with methotrexate. Cyclosporine was the only drug that showed a significant increased risk of serious infections compared with methotrexate (adjusted RR = 3.12, 95% CI = 1.1–8.8). Adalimumab in combination with methotrexate had the highest risk of infection recurrence (adjusted RR = 4.33, 95% CI = 2.27–8.24). More data are needed regarding the safety of combining biological drugs and methotrexate in psoriasis patients.

Finally, our study showed no significant change over time in the incidence rate of infections between patients taking methotrexate and patients taking other drugs or drug combinations. Unlike the reported risk in rheumatoid arthritis, infection risk in psoriasis patients under biologics therapy does not seem to be higher during the first year of use.

MATERIALS AND METHODS

This study was based on data from BIOBADADERM, a multicenter, prospective cohort study in clinical practice. BIOBADADERM has been previously described (Carrascosa et al., 2013; Garcia-Doval et al., 2012; Sanchez-Moya et al., 2013). All patients gave written informed consent to participate. The study was approved by an ethics committee and performed in compliance with the Declaration of Helsinki and local regulations.

Twelve dermatology departments across Spain participated. BIOBADADERM began in 2008. We included all prospective data from January 2008 through November 2015. Biologics have been commercially available in Spain since 2005. The National Health System covers the cost of all study drugs in most circumstances.

All patients with moderate to severe psoriasis who started a therapy with biologics (incident users for the specific drug) in participating centers were included in BIOBADADERM. As a comparison group, a systematic sample of psoriasis patients receiving nonbiological systemic therapy for the first time was collected. These were patients who started a course of methotrexate, cyclosporine, or acitretin after January 2008. Once patients in this group received a biological drug, they were moved to the biologics group. The treating physician determined the treatment dose.

The only exclusion criterion was the patient's refusal to participate. Patient follow-up continued as long as possible. All participants were monitored at least once a year, but several visits during a year were commonly made as part of usual care. Any adverse events were included in the database if they were serious or led to a change in therapy or to an unplanned health care demand. To ensure high quality data, BIOBADADERM monitors the clinical records from each center periodically.

The use of the BIOBADADERM registry for this study, including protocol and materials, has been approved by the Spanish Agency of Medicines and Health Products (AEMPS) and Ethics Committee of the Hospital 12 de Octubre in Madrid (216/07).

Statistical analysis

Data were analyzed using Stata 14.1 (StataCorp, College Station, TX). Demographic and descriptive data were presented as proportions in discrete quantitative variables and as mean and standard deviation in continuous quantitative data. To handle

missing data, we use a complete-case analysis, because we assume that the missing data pattern was Missing at Random.

Serious infections are those that resulted in death, were life-threatening, required prolonged hospitalization, or caused persistent disability.

We considered an infection as recurrent if the patient had already experienced another infection during therapy with the same drug.

We used methotrexate as the comparator with all the drugs (included classics and biologics) because it represents a standard of therapy and the largest group among classic therapies. We produced crude rates of infection and crude risk ratios of infection, serious infections, and recurrent infections compared with methotrexate.

To reduce the bias from noncontrol of treatment assignment in the nonrandomized cases, we calculated the propensity score of indication for each drug compared with methotrexate. In our study, we used all the covariates recorded to create a propensity score for each drug and then included it in the multivariable analysis, as an extra step to minimize potential bias in our cohort study as much as possible.

Adjusted RRs were calculated using Poisson regression with robust standard errors to take into account clustering of outcomes by patient. We used a Poisson mixed-model regression considering the center as a random effect to take into account within-center clustering of patients. Initially, we included all the covariates that appeared to be significantly associated with the outcome in the analysis of each drug, but in the final model, we included only those that significantly improved the model fit using the likelihood ratio test. Age, sex, and propensity score for each drug were included in the final model independent of the likelihood ratio test. We performed a sensitivity analysis with a fully adjusted multivariate model (see [Supplementary Table S3](#) online).

We also checked the assumption, under the Poisson regression, of the RR of infection compared with methotrexate remaining constant over time by splitting the follow-up time into small intervals and plotting the RR with a 95% CI for each drug in each of these time units.

We calculated the number of patients needed for statistical power to detect differences in comparison with methotrexate. We computed a number needed to harm for one infection, one serious infection, and one recurrent infection for each drug (see [Supplementary Table S4](#) online), by using raw rates of infection.

Adverse events were assigned to a drug if they occurred during drug therapy or within a 90-day period after the last dose. If an event could be associated with several drugs, it was associated with all of them. We compared this method (90 days) with time from discontinuation plus two half-lives of each drug, and the results were virtually identical in the number of infections assigned to each drug.

To analyze periods of exposure to more than one biological drug, a new period of exposure called “combined exposure” was created, and the infection was assigned to the combination therapy group.

At least 78 events were required in both groups to detect a relative risk of 2.0, assuming a power of 80% and alpha risk of 5%. Our study had a power of greater than 80% to detect a 2-fold increase in the risk of overall infection and recurrent infections. However, the power to detect an RR of 2.0 in the rate of serious infections was less than 60%.

ORCID

Ignacio Garcia-Doval: <http://orcid.org/0000-0002-6881-5260>

CONFLICT OF INTEREST

Dávila-Seijo received travel grants for congresses from Pfizer and Janssen. Daudén served as a consultant for AbbVie Laboratories, Amgen, Astellas, Celgene, Centocor Ortho Biotech Inc., Galderma, Glaxo, Janssen-Cilag, Leo Pharma, MSD, Novartis, and Pfizer Inc.; received honoraria from Abbott Laboratories, Amgen, Celgene, Janssen-Cilag Pty. Ltd., Leo Pharma, MSD, Novartis, and Pfizer Inc.; participated in speakers' bureaus for AbbVie Laboratories, Janssen Pharmaceuticals Inc., MSD, and Pfizer Inc.; and received grants from AbbVie Laboratories, Janssen Pharmaceuticals Inc., and Pfizer Inc. Carretero served as a consultant and investigator for AbbVie Laboratories, Janssen-Cilag Pty. Ltd., MSD, and Pfizer Inc. and received grants from Abbott, Janssen, and Pfizer, as well as equipment from MSD and Pfizer Inc. Carrascosa served as a consultant and speaker for AbbVie Laboratories, Janssen Pharmaceuticals Inc., MSD, Pfizer-Wyeth, Novartis, and Celgene. Ferrándiz served as a consultant and/or speaker for AbbVie Laboratories, Janssen Pharmaceuticals Inc., Pfizer, Celgene, and Almirall SA and received grants from AbbVie Laboratories. Vanaclocha participated as speaker for AbbVie Laboratories, Pfizer Inc., MSD, and Janssen Pharmaceuticals Inc. Herrera-Ceballos served as a consultant and speaker for AbbVie Laboratories, Janssen Pharmaceuticals Inc., and Pfizer-Wyeth. de la Cueva acted as a consultant for Janssen-Cilag, AbbVie, MSD, Pfizer, and Leo-Pharma. Belinchón acted as a consultant for Pfizer-Wyeth, Janssen Pharmaceuticals Inc., MSD, Almirall SA, and Leo-Pharma and as a speaker for AbbVie, Pfizer-Wyeth, Janssen Pharmaceuticals Inc., and MSD. Sánchez-Carazo acted as a consultant for AbbVie Laboratories, Janssen Pharmaceuticals Inc., MSD, and Pfizer-Wyeth. Alsina acted as a consultant for AbbVie Laboratories and Merck/Schering-Plough. López-Estebananz served as a consultant for Abbott Laboratories, Janssen Pharmaceuticals Inc., MSD, and Pfizer-Wyeth and as a speaker for AbbVie Laboratories, Janssen Pharmaceuticals Inc., MSD, and Pfizer-Wyeth. Garcia-Doval received travel grants for congresses from Merck/Schering-Plough Pharmaceuticals, Pfizer, and Janssen.

ACKNOWLEDGMENTS

This work was conducted within the BIOBADADERM Study Group. The following members participated in acquisition of data and review of the manuscript: Beatriz Pérez Zafrilla (Unidad de Investigación, Fundación AEDV) and Carlos Muñoz-Santos (Hospital Clinic of Barcelona, Barcelona, Spain); Victoria Mendiola-Fernández and Cristina Sánchez Roldán (Hospital Universitario Virgen de la Victoria, Malaga, Spain); Diana Ruiz-Genao and Begoña Echeverría (Hospital Universitario Fundación Alcorcón, Madrid, Spain), and Sagrario Galiano Mejías (Hospital Universitario Infanta Leonor, Madrid, Spain).

Disclaimer

The BIOBADADERM project is sponsored by the Fundación Academia Española de Dermatología y Venereología, which receives financial support from the Spanish Medicines and Health Products Agency (Agencia Española de Medicamento y Productos Sanitarios) and from pharmaceutical companies (Abbott/AbbVie, Pfizer, MSD, and Janssen). Novartis gave financial support for this study. Collaborating pharmaceutical companies have not participated in the analysis or interpretation of the data.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at <http://dx.doi.org/10.1016/j.jid.2016.08.034>.

REFERENCES

Andersen NN, Jess T. Risk of infections associated with biological treatment in inflammatory bowel disease. *World J Gastroenterol* 2014;20:16014–9.

Armstrong AW, Bagel J, Van Voorhees AS, Robertson AD, Yamauchi PS. Combining biologic therapies with other systemic treatments in psoriasis: evidence-based, best-practice recommendations from the Medical Board of the National Psoriasis Foundation. *JAMA Dermatol* 2015;151:432–8.

Atzeni F, Sarzi-Puttini P, Botsios C, Carletto A, Cipriani P, Favalli EG, et al. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: comparison of adalimumab, etanercept and infliximab in the GISEA registry. *Autoimmun Rev* 2012;12:225–9.

Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients

with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.

Carrascosa JM, Vilavella M, Garcia-Doval I, Carretero G, Vanaclocha F, Dauden E, et al. Body mass index in patients with moderate-to-severe psoriasis in Spain and its impact as an independent risk factor for therapy withdrawal: results of the Biobadaderm Registry. *J Eur Acad Dermatol Venereol* 2013;28:907–14.

Cather JC, Crowley JJ. Use of biologic agents in combination with other therapies for the treatment of psoriasis. *Am J Clin Dermatol* 2014;15:467–78.

Ferrándiz C, Carrascosa JM, Toro M. Prevalence of psoriasis in Spain in the age of biologics. *Actas dermosifiliogr* 2014;105:504–9.

Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology* 2011;50:124–31.

García-Doval I, Carretero G, Vanaclocha F, Ferrándiz C, Dauden E, Sanchez-Carazo JL, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. *Arch Dermatol* 2012;148:463–70.

García-Doval I, Hernandez MV, Vanaclocha F, Sellas A, de la Cueva P, Montero D, et al. Should TNF-antagonists safety information be applied from patients with rheumatoid arthritis to psoriasis? Rates of serious adverse events in the prospective rheumatoid arthritis Biobadaderm and psoriasis Biobadaderm cohorts [e-pub ahead of print]. *Br J Dermatol* 2016. <http://dx.doi.org/10.1111/bjd.14776> (accessed 6 March 2016).

Gordon KB, Papp KA, Langley RG, Ho V, Kimball AB, Guzzo C, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (Part II of II): results from analyses of infections and malignancy from pooled phase II and III clinical trials. *J Am Acad Dermatol* 2012;66:742–51.

Greenberg JD, Reed G, Kremer JM, Tindall E, Kavanaugh A, Zheng C, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis* 2010;69:380–6.

Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the psoriasis longitudinal assessment and registry (PSOLAR). *JAMA Dermatol* 2015;151:961–9.

Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris—Update 2015—Short version—EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2015;29:2277–94.

Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013;133:377–85.

Reich K, Papp KA, Griffiths CE, Szapary PO, Yeilding N, Wasfi Y, et al. An update on the long-term safety experience of ustekinumab: results from the psoriasis clinical development program with up to four years of follow-up. *J Drugs Dermatol* 2012;11:300–12.

Sakai R, Komano Y, Tanaka M, Nanki T, Koike R, Nagasawa H, et al. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. *Arthritis Care Res* 2012;64:1125–34.

Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, et al. Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. *Rheumatology* 2007;46:327–34.

Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2011;70:616–23.

Sanchez-Moya AI, Garcia-Doval I, Carretero G, Sanchez-Carazo J, Ferrándiz C, Herrera Ceballos E, et al. Latent tuberculosis infection and active tuberculosis in patients with psoriasis: a study on the incidence of tuberculosis and the prevalence of latent tuberculosis disease in patients with moderate-severe psoriasis in Spain. *BIOBADADERM registry. J Eur Acad Dermatol Venereol* 2013;27:1366–74.

- Schmitt J, Rosumeck S, Thomaschewski G, Sporbeck B, Haufe E, Nast A. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol* 2014;170:274–303.
- Shalom G, Zisman D, Bitterman H, Harman-Boehm I, Greenberg-Dotan S, Dreier J, et al. Systemic therapy for psoriasis and the risk of herpes zoster: a 500,000 person-year study. *JAMA Dermatol* 2015;151:533–8.
- Soderlin M, Blomkvist C, Dahl P, Forsberg P, Fohlman J. [Increased risk of infection with biological immunomodifying antirheumatic agents. Clear guidelines are necessary as shown by case reports]. *Lakartidningen* 2005;102:3794–6, 3799–800.
- Suwannalai P, Auethavekiat P, Udomsubpayakul U, Janvitayanujit S. The infectious profiles of anti-tumor necrosis factor agents in a Thai population: a retrospective study at the university-based hospital. *Int J Rheum Dis* 2009;12:118–24.
- Trautmann M. [A new clinical disease entity. Tuberculosis in users of TNF-alpha inhibitors]. *Pharm Unserer Zeit* 2012;41:79–83.
- Trotta F, Valentini G. [Safety of anti-TNFalpha biological drugs]. *Reumatismo* 2005;57:34–9.
- van Dartel SA, Franssen J, Kievit W, Flendrie M, den Broeder AA, Visser H, et al. Difference in the risk of serious infections in patients with rheumatoid arthritis treated with adalimumab, infliximab and etanercept: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Ann Rheum Dis* 2013;72:895–900.
- Wakkee M, de Vries E, van den Haak P, Nijsten T. Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. *J Am Acad Dermatol* 2011;65:1135–44.
- Wood KL, Hage CA, Knox KS, Kleiman MB, Sannuti A, Day RB, et al. Histoplasmosis after treatment with anti-tumor necrosis factor-alpha therapy. *Am J Respir Crit Care Med* 2003;167:1279–82.
- Yiu ZZ, Exton LS, Jabbar-Lopez Z, Mohd Mustapa MF, Samarasekera EJ, Burden AD, et al. Risk of serious infections in patients with psoriasis on biologic therapies: a systematic review and meta-analysis. *J Invest Dermatol* 2016;136:1584–91.