Accepted Manuscript

Change over time in the rates of adverse events in patients receiving systemic therapy for psoriasis: a cohort study

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PII: S0190-9622(17)32683-X

DOI: 10.1016/j.jaad.2017.10.051

Reference: YMJD 12121

To appear in: *Journal of American Dermatology*

Received Date: 28 September 2017

Revised Date: 25 October 2017

Accepted Date: 29 October 2017

Please cite this article as: Descalzo MA, Carretero G, Ferrándiz C, Rivera R, Daudén E, Gómez-García FJ, de la Cueva P, Herrera-Ceballos E, Belinchón I, López-Estebaranz JL, Alsina M, Sánchez-Carazo JL, Ferrán M, Baniandrés O, Carrascosa JM, Llamas-Velasco M, Ruiz-Genao D, Herrera-Acosta E, Muñoz-Santos C, García-Doval I, Biobadaderm Study Group, Change over time in the rates of adverse events in patients receiving systemic therapy for psoriasis: a cohort study, *Journal of American Dermatology* (2017), doi: 10.1016/j.jaad.2017.10.051.

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Target Journal: JAAD Research letter; max. words 500

Text word count: 492; **References:** 5; **Tables and figures:** 2 table

IRB status: Observational study. Approved (Biobadaderm: Hospital Universitario 12 de Octubre (216/07).

Attachments: STROBE checklist

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Conflict of interest:

Dr Carretero has been reimbursed by Janssen, Abbvie, Novartis, Pfizer, MSD and Celgene for advisory service and conference.

Dr Ferrándiz has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Amgen, Celgene, Centocor, Janssen-Cilag, LEO Pharma, Lilly, Merck Sharp & Dohme, Novartis and Pfizer.

Dr Rivera participated in a speaker's bureau for Abbott, Janssen, MSD and Pfizer-Wyeth.

Dr Dauden acted as consultant for Abbott, Amgen, Astellas, Centocor Ortho Biotech Inc, Galderma, Glaxo, Jansenn-Cilag, Leo Pharma, Novartis, Pfizer, MSD and Celgene, received honoraria form Abbott, Amgen, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, MSD, Celgene, participated in a speakers bureau for Abbott, Pfizer, MSD and Janssen and received grants from Pfizer, Abbott, Janssen and MSD.

Dr De la Cueva acted as a consultant and speaker for Janssen-Cilag, AbbVie, MSD, Pfizer, Novartis, Lilly, Almirall and Leo-Pharma.

Dr. E. Herrera-Ceballos has served as a consultant and/or speaker for and/or participated in clinical trials as IP and sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Janssen-Cilag, LEO Pharma, Lilly, Novartis and Pfizer.

Dr Belinchón acted as a consultant for Pfizer-Wyeth; Janssen Pharmaceuticals Inc, MSD, Almirall SA, Lilly and Leo-Pharma, and as an invited speaker for AbbVie, Pfizer-Wyeth, Janssen Pharmaceuticals Inc , Novartis and MSD.

Dr López-Estebaranz participated as AB and received educational grants from Janssen, Abbvie, MSD, Lilly, Novartis, LeoPharma, Pfizer.

Dr Alsina gave expert testimony for Merck-Schering Plough and Abbott.

Dr Carrascosa has participated as speaker and/or advisor for Celgene, Janssen, Lilly, Novartis, Leo Pharma, Pfizer, MSD, Abbvie, Biogen Amgen.

Dr Ferran acted as a consultant for Abbott, Janssen, MSD and Pfizer-Wyeth, participated in a speaker's bureau for MSD and Janssen, and received grants from Serono.

Dr Baniandrés acted as consultant for Abbvie, Janssen, Pfizer-Wyeth and Novartis.

Dr. E. Herrera-Acosta has served as consultant and/or speaker with Leo Pharma, Novartis, Janssen, Lilly, Celgene y Abbvie.

Dr Muñoz-Santos acted as a consultant for Abbott, Janssen, and Pfizer received honoraria from Abbott, Janssen, Merck Pfizer-Wyeth and Schering-Plough, gave expert testimony for Abbott, Janssen, Wyeth and Schering-Plough, and received grants from Janssen and Wyeth.

Dr Garcia-Doval received travel grants for congresses from MSD, Pfizer and Schering.

None of the other authors has any conflicting interests to declare.

Abbreviations:

SAE: Serious Adverse Events

IR: Incidence Rate

89 IRR: Incidence Rate Ratio

90 **Keywords:** Psoriasis/drug therapy, Biological agents, Anti-Inflammatory Agents,
91 Immunosuppressive Agents, Safety, anti-TNF, time trends, adverse effects, incidence
92 rate, serious adverse events, “Diagnostic Tests, Routine”.

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To the Editor: It is not well established how the incidence of adverse events in psoriatic patients treated with systemic drugs varies over time. Information on trends in adverse events would be useful in clinical practice to inform the frequency of follow-up visits and lab tests. Our objective was to describe the incidence of adverse events over time.

We used a cohort of psoriatic patients receiving systemic therapy, BIOBADADERM[1], to calculate the incidence rate (IR) of adverse events by period of time. IR ratios (IRR) were obtained using a Poisson mixed-model regression considering the centre as a random effect to take into account within-centre clustering of patients. Data included 2084 patients and 7282 person-years with 5018 adverse events. Detailed baseline characteristics of patients exposed to each drug are described in table 1. Some drugs, such as cyclosporine or infliximab were associated with higher rates of overall adverse events. For most drugs, rates of overall adverse events were higher in the first year (table 2). This first-year peak was especially marked for cyclosporine although it is barely used beyond 1 year. If we focus on serious adverse events (SAE), rates were much lower compared to overall adverse events, and were higher for cyclosporine and infliximab overall. Rates of abnormal laboratory results showed an increase in the first year in classic drugs whereas for biologic drugs the incidence stayed constant over time.

We found that overall rates of adverse events were higher during the first year of treatment in all drugs.

One explanation for the pattern of some adverse events being higher in the first year could be explained by information bias, as patients may be more likely to report

adverse events in the first year of treatment[2]. Our results are also consistent with previous studies reporting adverse events[3]. One hypothesis suggests that patients susceptible to adverse events have their treatment terminated within the first year, resulting in a survivor effect to explain the pattern of adverse effects[4]. After the first year, the remaining population would be less susceptible and therefore rates of adverse effects would remain constant. Rates of SAE were constant over time for all drugs, and it seems likely that most of them were not detected by planned visits, but were the cause of an unplanned demand for care[5].

Our findings provide evidence for planning follow-up visits that should be more intensive in the first year for all drugs. This is more relevant for patients receiving classic systemic drugs, when well-known side effects are more likely to appear. Some drugs, such as cyclosporine or infliximab, might require more intensive follow-up. After this first year, less intense and evenly spaced reviews and testing seem appropriate (indefinitelyr or at least for the first 3 years of treatment in agreement with our data). Rates of SAE are also constant over time for all drugs, so the effort to detect them should be constant although they might not be detected by routine visits, but lead to unexpected consultations.

Funding sources: The BIOBADADERM project is promoted by the Fundación Piel Sana Academia Española de Dermatología y Venereología, which receives financial support from the Spanish Medicines and Health Products Agency (Agencia Española de Medicamentos y Productos Sanitarios) and from pharmaceutical companies (Abbott/Abbvie, Pfizer, MSD, Novartis, Lilly and Janssen).

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TABLES

Table 1. - Descriptive characteristics of the active compound. Patients included in the BIOBADADERM cohort (2008-2016).

	Etanercept	Infliximab	Adalimumab	Ustekinumab	Acitretin	Cyclosporine	Methotrexate
Number of patients	486	101	498	457	478	443	824
Number of treatments cycles	792	130	761	628	650	586	1190
Lost to follow-up. n (%)	46 (9)	5 (5)	46 (9)	44 (10)	81 (17)	53 (12)	133 (16)
Duration of exposure (years), median	0.99	1.33	1.17	1.64	0.57	0.36	0.66
Duration of exposure (years): interquartile range	0.46-2.22	0.51-3.43	0.51-2.68	0.76-3.8	0.26-1.38	0.2-0.75	0.33-1.65
Women. n (%)	211 (43)	36 (36)	191 (38)	199 (44)	158 (33)	212 (48)	377 (46)
Plaque psoriasis. n (%)	469 (97)	92 (91)	470 (94)	437 (96)	407 (85)	398 (90)	758 (92)
Psoriatic arthritis. n (%)	88 (18)	26 (26)	98 (20)	55 (12)	30 (6)	32 (7)	79 (10)
Age (years), mean (SD)	52 (14.7)	49.5 (12.1)	49.3 (13.5)	49.6 (14.4)	57 (15.1)	45.8 (13.9)	50.6 (14.8)
Duration of disease at start of treatment (years), mean (SD)	17.8 (12.9)	17.2 (11.4)	17.4 (11.6)	17.6 (12.3)	15.6 (14.3)	13.9 (11.4)	14.9 (13.1)
PASI, mean (SD)	13.1 (8.2)	16.6 (9.5)	14.4 (8.5)	15.4 (9.3)	10.1 (6.9)	13.1 (8.7)	10 (6.5)

Table 2. Rates of adverse events by year and drug.

	All adverse events		**Serious adverse events**		**Altered test results (Investigations SOC)**	
Methotrexate	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**
Year 1	1206 (1131-1286)	1 (reference)	112 (91-139)	1 (reference)	154 (129-185)	1 (reference)
Year 2	843 (750-947)	0.7 (0.61-0.8)***	93 (65-132)	0.83 (0.55-1.25)	54 (34-86)	0.35 (0.21-0.57)***
Year 3	700 (590-830)	0.58 (0.48-0.7)***	117 (77-177)	1.04 (0.65-1.66)	37 (18-78)	0.24 (0.11-0.52)***
Cyclosporine	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**
Year 1	2212 (2042-2396)	1 (reference)	228 (178-292)	1 (reference)	309 (249-382)	1 (reference)
Year 2	693 (497-965)	0.31 (0.22-0.44)***	158 (79-317)	0.69 (0.33-1.45)	119 (53-264)	0.38 (0.17-0.88)*
Year 3	459 (219-963)	0.21 (0.1-0.44)***	-	-	197 (63-610)	0.64 (0.2-2.02)
Acitretin	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**
Year 1	1293 (1185-1411)	1 (reference)	170 (133-216)	1 (reference)	193 (154-242)	1 (reference)
Year 2	829 (697-986)	0.64 (0.53-0.78)***	111 (69-178)	0.65 (0.38-1.11)	104 (64-170)	0.54 (0.32-0.93)*
Year 3	902 (714-1140)	0.7 (0.54-0.9)**	168 (97-289)	0.99 (0.54-1.79)	39 (12-120)	0.2 (0.06-0.64)**
Etanercept	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**
Year 1	1015 (936-1100)	1 (reference)	104 (81-134)	1 (reference)	67 (49-91)	1 (reference)
Year 2	1046 (935-1169)	1.03 (0.9-1.18)	74 (49-113)	0.71 (0.44-1.16)	64 (41-100)	0.96 (0.56-1.67)
Year 3	969 (834-1126)	0.96 (0.81-1.13)	125 (83-190)	1.21 (0.74-1.96)	40 (19-84)	0.6 (0.27-1.34)
Infliximab	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**
Year 1	1776 (1532-2060)	1 (reference)	284 (196-412)	1 (reference)	203 (131-315)	1 (reference)
Year 2	1259 (1003-1582)	0.71 (0.54-0.93)*	221 (128-381)	0.78 (0.40-1.5)	51 (16-158)	0.25 (0.07-0.85)*
Year 3	695 (483-1000)	0.39 (0.26-0.58)***	96 (36-255)	0.33 (0.12-0.96)*	144 (65-320)	0.71 (0.28-1.76)
Adalimumab	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**
Year 1	1257 (1169-1351)	1 (reference)	170 (140-208)	1 (reference)	110 (86-141)	1 (reference)
Year 2	1001 (898-1116)	0.8 (0.7-0.91)**	133 (99-179)	0.78 (0.55-1.12)	111 (80-154)	1.01 (0.67-1.52)
Year 3	1058 (927-1208)	0.84 (0.72-0.98)*	159 (113-223)	0.93 (0.63-1.38)	115 (77-172)	1.05 (0.66-1.68)
Ustekinumab	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**	**Rate (CI95%)**	**IRR (CI95%)**
Year 1	942 (863-1028)	1 (reference)	120 (94-153)	1 (reference)	64 (45-89)	1 (reference)
Year 2	791 (702-892)	0.84 (0.72-0.97)*	71 (48-106)	0.59 (0.37-0.95)*	71 (48-106)	1.12 (0.66-1.88)
Year 3	619 (527-727)	0.66 (0.55-0.79)***	116 (80-169)	0.97 (0.62-1.51)	58 (34-98)	0.91 (0.49-1.7)

Rates per 1000 patient-years, IRR: Incidence Rate Ratio; *p-value<0.05; **p-value<0.01; ***p-value<0.001; CI: Confidence Interval, SOC: System Organ Classes