Accepted Manuscript

The risk of urinary tract infections in patients with psoriasis on systemic medications in Biobadaderm registry: a prospective cohort study

A. Sahuquillo-Torralba, MD, G. Carretero, MD, PhD, R. Rivera, MD, C. Ferrándiz, MD, PhD, E. Daudén, MD, PhD, P. de la Cueva, MD, PhD, F.J. Gómez-García, MD, I. Belinchón, MD, PhD, E. Herrera-Acosta, MD, D. Ruiz-Genao, MD, M. Ferrán, MD, M. Alsina, MD, PhD, J.L. Sánchez-Carazo, MD, PhD, O. Baniandrés, MD, PhD, L. Rodriguez, MD, J. Vilar, MD, C. García-Donoso, MD, J.M. Carrascosa, MD, PhD, M. Llamas-Velasco, MD, PhD, E. Herrera-Ceballos, MD, PhD, J.L. López-Estebaranz, MD, C. Pujol-Marco, MD, M.A. Descalzo, MSc, PhD, I. García-Doval, MD, PhD, Biobadaderm Study Group

PII: S0190-9622(19)32388-6

DOI: https://doi.org/10.1016/j.jaad.2019.07.028

Reference: YMJD 13636

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 22 May 2019

Revised Date: 3 July 2019

Accepted Date: 6 July 2019

Please cite this article as: Sahuquillo-Torralba A, Carretero G, Rivera R, Ferrándiz C, Daudén E, de la Cueva P, Gómez-García F, Belinchón I, Herrera-Acosta E, Ruiz-Genao D, Ferrán M, Alsina M, Sánchez-Carazo J, Baniandrés O, Rodriguez L, Vilar J, García-Donoso C, Carrascosa J, Llamas-Velasco M, Herrera-Ceballos E, López-Estebaranz J, Pujol-Marco C, Descalzo M, García-Doval I, Biobadaderm Study Group, The risk of urinary tract infections in patients with psoriasis on systemic medications in Biobadaderm registry: a prospective cohort study, *Journal of the American Academy of Dermatology* (2019), doi: https://doi.org/10.1016/j.jaad.2019.07.028.

Article type: *Research Letter*

Title: The risk of urinary tract infections in patients with psoriasis on systemic medications in Biobadaderm registry: a prospective cohort study

Authors:
A Sahuquillo-Torralba[1] , MD, G Carretero[2], MD, PhD, R Rivera[3], MD, C Ferrándiz[4], MD, PhD, E Daudén[5], MD, PhD, P de la Cueva[6], MD, PhD, FJ. Gómez-García[7], MD, I Belinchón[8], MD, PhD, E Herrera-Acosta[9], MD, D Ruiz-Genao[10], MD, M Ferrán[11], MD, M Alsina[12], MD, PhD, JL Sánchez-Carazo[13], MD, PhD, O Baniandrés[14], MD, PhD, L Rodriguez[15],MD, J Vilar[2], MD, C García-Donoso[3], MD, JM Carrascosa[4],MD,PhD, M Llamas-Velasco[5],MD,PhD, E Herrera-Ceballos[9], MD, PhD, JL López-Estebaranz[10], MD, C Pujol-Marco[18], MD, MA Descalzo[16], MSc, PhD, I García-Doval[16, 17] , MD, PhD, and Biobadaderm Study Group.

[1] Department of Dermatology, Hospital Universitario y Politécnico La Fe, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia, Spain.
[2] Department of Dermatology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain.
[3] Department of Dermatology, Hospital Universitario 12 de Octubre, Madrid, Spain.
[4] Department of Dermatology, Hospital Universitari Germans Trias i Pujol, Badalona, Universidad Autónoma de Barcelona, Barcelona, Spain.
[5] Department of Dermatology, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria La Princesa (IIS-IP), Madrid, Spain.
[6] Department of Dermatology, Hospital Universitario Infanta Leonor, Madrid, Spain.
[7] Department of Dermatology, Hospital Universitario Reina Sofía, Cordoba, Spain.
[8] Department of Dermatology, Hospital General Universitario de Alicante, Alicante, Spain.
[9] Department of Dermatology, Hospital Universitario Virgen de la Victoria, Málaga, Spain.
[10] Department of Dermatology, Fundación Hospital de Alcorcón, Madrid, Spain.
[11] Department of Dermatology, Hospital del Mar, Parc de Salut Mar, Barcelona, Spain.
[12] Department of Dermatology, Hospital Clínic de Barcelona, UB, Barcelona Spain.
[13] Department of Dermatology, Hospital General Universitario de Valencia, Valencia, Spain.
[14] Department of Dermatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain.
[15] Department of Dermatology. Hospital Virgen del Rocío, Sevilla. Spain.
[16] Research Unit. Fundación Piel Sana AEDV, Madrid, Spain.
[17] Department of Dermatology. Complexo Hospitalario Universitario de Vigo, Vigo. Spain.
[18] Department of Dermatology, Hospital Universitario y Politécnico La Fe, Valencia, Spain.

Corresponding author:

Antonio Sahuquillo-Torralba
Address: Fundación Piel Sana AEDV, Calle Ferraz 100, Madrid.
E-mail: saucodos@gmail.com

Funding:

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, Janssen and Almirall).

Collaborating pharmaceutical companies were not involved in the: design and conduct of the study; collection, management, analysis and interpretation of data; preparation, review, or approval of the manuscript; decision to submit the manuscript for publication.

Conflict of interest:

Dr Sahuquillo 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, Celgene, Janssen-Cilag, LEO Pharma, Lilly, Novartis and Pfizer.
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, Janssen-Cilag, LEO Pharma, Lilly, Merck Sharp & Dohme, Novartis Pfizer and Almirall.
Dr Rivera acted as consultant and/or speaker for and/or participated in clinical trials as IP for Abbvie, Almirall, Celgene, Janssen, Leo Pharma, Lilly, Novartis, 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/or speaker for Janssen-Cilag, AbbVie, MSD, Pfizer, Novartis, Lilly, Almirall, UCB, Biogen, Celgene, Amgen, Sandoz, Sanofi 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 speaker and/or advisor for Janssen Pharmaceuticals Inc, Almirall SA, Lilly, AbbVie, Novartis, Celgene, Biogen Amgen, Leo-Pharma, Pfizer-Wyeth, 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, Pfizer, Janssen, Novartis, Leo Pharma, Almirall and Abbott.
Dr Carrascosa has participated as speaker and/or advisor for Celgene, Janssen, Lilly, Novartis, Leo Pharma, Pfizer, MSD, Abbvie, Biogen Amgen.
Dr Llamas acted as a consultant and speaker for Janssen-Cilag, AbbVie, Celgene, Pfizer, Novartis, Lilly, Almirall and Leo-Pharma and has participated in clinical assays.
Dr Ferran has participated as speaker and/or advisor for Janssen, Lilly, Novartis, Pfizer, MSD, Abbvie Celgene and Almirall,
Dr Baniandrés acted as a consultant and/or speaker for Janssen-Cilag, AbbVie, Pfizer, Novartis, Lilly and Almirall.
Dr. E. Herrera-Acosta has served as consultant and/or speaker with Leo Pharma, Novartis, Janssen, Lilly, Celgene y Abbvie.
Dr Garcia-Doval received travel grants for congresses from Abbvie, MSD and Pfizer.
Dra Rodriguez Fernandez-Freire acted as a consultant and speaker for Janssen-Cilag, AbbVie, MSD, Pfizer, Novartis, Lilly, Almirall, Celgene and Leo-Pharma.
Dr Ruiz-Genao has been reimbursed by Pfizer, Jansse, Celgene, Abbvie, Novartis and LeoPharma for advisory services and conferences.

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

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

Manuscript word: 500 (excluding capsule summary, references, tables)

Tables: 1

Figures: 0

Supplementary figures: 0

Supplementary tables: 0

Attachments: CONSORT checklist

References: 4

Keywords: psoriasis patients, risk of urinary infections, psoriasis treatments, Biobadaderm registry.

Clinical trials and real-life evidence show that the use of biological treatments in psoriasis patients portends an increased risk of developing infections[1, 2].

Biobadaderm is a multicentre prospective cohort, with the objective of evaluating the safety of systemic therapy for psoriasis [2]. Once a year, reports are created. In 2018, a signal regarding symptomatic urinary tract infection (UTI) was detected.

Our primary objective was to describe the rates of clinical bacterial UTI in psoriasis patients undergoing systemic treatment compared to those being treated with methotrexate.

Sixteen hospitals throughout Spain participated. The study period ranged from October 2008 to November 2018. All bacterial UTIs were registered and classified as afebrile UTI (cystitis) and febrile UTI (pyelonephritis and prostatitis) using the MedDRA dictionary. The patients on combination therapy were excluded. We estimated the crude rates of symptomatic bacterial UTI in patients receiving specific systemic drugs and compared them to those treated with methotrexate. Adjusted rate ratios(aRR) were obtained using a robust multilevel Poisson model including age, gender, diabetes status, treatment order, and propensity score (i.e., including all variables associated with drug selection) for each drug. Specific aRRs were obtained according to gender. Anti-IL17 drugs were analyzed as a group due to low sample size; apremilast and fumaric acid esters were not included.

A total of 3,013 patients exposed to systemic drugs were included, with 9,585 patients-years of follow-up. The number of patients exposed to each drug is detailed in table 1. In patients exposed to biologics, 91 UTIs were reported, of

which only five (5%) were serious (0.74 serious UTIs [95% CI: 0.31-1.78] cases per 1000 patient-years). In patients receiving methotrexate treatment, 19 UTIs were reported, of which three (16%) were serious (1.74 [95% CI: 0.56-5.39]). The overall aRR of UTIs between biologics and methotrexate was 1.01 (95% CI: 0.74-1.39). No differences in the risk of serious UTIs between patients exposed to biologics compared to patients treated with methotrexate were observed.

When gender was taken into account, significant results were limited to women, and aRR showed increased risks of UTIs in women for cyclosporine (only for non-febrile), infliximab, and anti-IL17, and decreased risks for acitretin (Table 1). Most of them were not serious.

The main limitation of this study is that it assesses a short period of exposure to anti-IL17 and these drugs are evaluated as a single group. The increased risks detected in this study could be due to chance or selection bias, and should be confirmed or disputed by other studies.

Based on our findings, the use of cyclosporine, infliximab and anti-IL17 could be associated with a higher risk of symptomatic UTI in women. Given the increased risk shown by our results (approximately 20 extra cases per 1000 person-years), an appropriate strategy for women receiving these drugs should be devised, instructing them about warning signs. Only patients who show the warning signs should receive specific testing and treatment, because screening for detection and treatment of asymptomatic bacteriuria is only recommended in pregnant women and after high-risk urological surgery [3, 4].

References:

1. Garcia-Doval I, Cohen AD, Cazzaniga S,et al. Risk of serious infections, cutaneous bacterial infections, and granulomatous infections in patients with psoriasis treated with anti-tumor necrosis factor agents versus classic therapies: Prospective meta-analysis of Psonet registries. J Am Acad Dermatol. 2017;76; 299-308.

2. Davila-Seijo P, Dauden E, Descalzo MA, et al. Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry. J Invest Dermatol. 2017;137; 313-321.

3. Nicolle LE, Gupta K, Bradley SF,et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of Americaa. Clin Infect Dis. 2019. [Epub ahead of print]

4. de Cueto M, Aliaga L, Alos JI,et al. Executive summary of the diagnosis and treatment of urinary tract infection: Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). Enferm Infecc Microbiol Clin. 2017;35;314-320.

		All urinary bacterial infections				Afebrile urinary bacterial infections				Febrile urinary bacterial infections			
	Patient-years	Cases	Rate per 1000 p-y (95% CI)	Adjusted RR compared to methotrexate (95% CI)		Cases	Rate per 1000 p-y (95% CI)	Adjusted RR compared to methotrexate (95% CI)		Cases	Rate per 1000 p-y (95% CI)	Adjusted RR compared to methotrexate (95% CI)	
				Men	Women			Men	Women			Men	Women
Methotrexate	1726	19	11.01(7.02-17.25)	Reference	Reference	12	6.95 (3.95-12.24)	Reference	Reference	7	4.05 (1.93-8.51)	Reference	Reference
Acitretin	798	7	8.77(4.18-18.40)	1.35(0.38-4.78)	0.35(0.12-0.98)*	6	7.52 (3.38-16.74)	2.48 (0.65-9.54)	0.35 (0.09-1.33)	1	1.25 (0.18-8.90)	NA	**0.38 (0.19-0.77) ****
Cyclosporine	310	8	25.78(12.89-51.55)	1.08(0.15-7.56)	5.08(2.40-10.79)***	6	19.34 (8.69-43.04)	NA	**6.64 (2.11-20.83) ****	2	6.45 (1.61-25.77)	3.30 (0.64-16.93)	2.14 (0.64-7.17)
All biologics	6751	91	13.48(10.98-16.55)	0.98(0.53-1.82)	1.04(0.80-1.36)	76	11.26 (8.99-14.10)	1.16 (0.45-2.95)	1.38 (0.79-2.40)	15	2.22 (1.34-3.69)	0.73 (0.21-2.48)	0.46 (0.17-1.27)
Anti-TNF	3972	48	12.08(9.11-16.03)	1.14(0.66-1.95)	1.01(0.69-1.49)	38	9.57 (6.96-13.15)	1.28 (0.47-3.44)	1.34 (0.73-2.47)	10	2.52 (1.35-4.68)	0.82 (0.20-3.48)	**0.52 (0.27-0.98) ***
Etanercept	1682	19	11.29(7.20-17.71)	1.16(0.48-2.82)	1.02(0.39-2.68)	17	10.10 (6.28-16.25)	1.86 (0.62-5.63)	1.34 (0.48-3.74)	2	1.19 (0.30-4.75)	NA	0.55 (0.14-2.18)
Adalimumab	1948	23	11.81(7.85-17.77)	1.10(0.55-2.20)	0.74(0.46-1.19)	16	8.21 (5.03-13.41)	0.63 (0.24-1.63)	0.59 (0.26-1.32)	7	3.59 (1.71-7.54)	1.42 (0.38-5.25)	1.04 (0.44-2.46)
Infliximab	342	6	17.55(7.89-39.07)	1.56(0.25-9.73)	5.51(1.08-28.22)*	5	14.63 (6.09-35.14)	0.53 (0-122.82)	**7.02 (1.05-47.01) ***	1	2.93 (0.41-20.77)	3.39 (0.48-23.88)	NA
Anti-IL17	466	10	21.48(11.56-39.92)	0.90(0.34-2.40)	3.65(1.44-9.29)**	7	15.03 (7.17-31.54)	NA	**2.88 (1.17-7.10) ***	3	6.44 (2.08-19.98)	1.51 (0.50-4.57)	**10 (2.63-38.00) *****

Ustekinumab	2313	33	14.27(10.14-20.07)	0.91(0.33-2.47)	1.14(0.70-1.87)	31	13.40 (9.43-19.06)	0.92 (0.23-3.67)	1.54 (0.62-3.84)	2	0.86 (0.22-3.46)	0.64 (0.18-2.24)	0.27 (0.05-1.33)

Tables:

Table 1. Rates and relative risks of urinary bacterial infection in patients with psoriasis treated with systemic therapy

*p<0.05; **p<0.01; ***p<0.001
RR, Rate Ratio; P-Y, Patient-years; CI, Confidence Intervals; NA, Not Available