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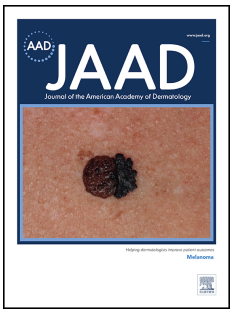

Incidence of severe COVID-19 outcomes in psoriatic patients treated with systemic therapies during the pandemic: a Biobadaderm cohort analysis

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Running head: Psoriasis, systemic therapy and COVID-19

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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 Baniandrés-Rodríguez acted as a consultant and/or speaker for Janssen-Cilag, AbbVie, Pfizer, Novartis, Lilly, Celgene, Leo Pharma and Almirall.
- Dr Vilar-Alejo participated as AB from Janssen, Novartis, AbbVie, Almirall and Celgene.
- 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 Carrascosa has participated as speaker and/or advisor for Celgene, Janssen, Lilly, Novartis, Leo Pharma, Pfizer, MSD, Abbvie, Biogen Amgen.
- 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 Herrera-Acosta has served as consultant and/or speaker with Leo Pharma, Novartis, Janssen, Lilly, Celgene y Abbvie.
- 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 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 López-Estebaranz participated as AB and received educational grants from Janssen, Abbvie, MSD, Lilly, Novartis, LeoPharma, Pfizer.
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including Janssen Pharmaceuticals Inc, Almirall SA, Lilly, AbbVie, Novartis, Celgene, Biogen Amgen, Leo-Pharma, UCB, Pfizer-Wyeth, and MSD.

- Dr Ferran-Farrés has participated as speaker and/or advisor for Janssen, Lilly, Novartis, Pfizer, MSD, Abbvie Celgene and Almirall.
- Dr Alsina gave expert testimony for Merck-Schering Plough, Pfizer, Janssen, Novartis, Lilly and Abbott, and has participated as speaker for Almirall, Janssen and Gebro Pharma.
- Dr Rodriguez Fernandez-Freire acted as a consultant and speaker for Janssen-Cilag, AbbVie, MSD, Pfizer, Novartis, Lilly, Almirall, Celgene and Leo-Pharma.
- Dr Carretero has been reimbursed by Janssen, Abbvie, Novartis, Pfizer, MSD and Celgene for advisory service and conference.
- Dr García-Donoso participated as AB from AbbVie, Almirall and speaker for Janssen, Lilly and Celgene.
- Dr Llamas-Velasco acted as a consultant and speaker and participated in clinical trials for Janssen-Cilag, AbbVie, Celgene, Pfizer, Novartis, Lilly, Almirall and Leo-Pharma.
- Dr 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 Botella-Estrada 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.
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None of the other authors has any conflicting interests to declare.

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The use of systemic treatments in psoriatic patients during the pandemic has been the subject of extensive debate. In March 2020, we performed a specific study within the cohort of Biobadaderm Registry, a previously described national, multicenter, prospective cohort [1]. Our primary objective was to analyze the incidence of COVID-19 infections and severe outcomes in a cohort of psoriatic patients treated with systemic therapies and to compare it to the general population.

We reviewed all Biobadaderm patient records and contacted the patients when needed. We collected information about current comorbidities related to COVID-19 and COVID-19 outcomes in all active patients of the registry. We used the latest data updated on 6 July 2020. We estimated the age and sex standardized incidence ratio (SIR) defined as the ratio of the observed cases to the expected number of cases according to the Spanish population. The main analysis examined hospitalization, ICU and death in PCR-confirmed patients included in Biobadaderm as compared to PCR-confirmed cases published by the Spanish Ministry of Health [2]. Also 95% CI were calculated for each SIR to compare significance between the Spanish figures and Biobadaderm.

In our study, we found that out of 2329 current active patients with systemic therapy, 73 patients (3.13%) had suffered from COVID-19, 13 patients (0.56%) required hospitalization, 1 patient (0.04%) needed ICU and 1 (0.04%) patient died. Patient characteristics are detailed in Table 1. The profile of COVID-19 cases was similar to that of the population of origin (Biobadaderm) in age and sex [3], but with higher percentages of comorbidities like hypertension (27% vs 22%) or diabetes mellitus (16% vs 11%).

In our main analysis (Table 2), the SIR for COVID-19 infection, hospitalization, ICU and death were slightly higher in psoriatic patients treated with systemic therapies compared to the general population of Spain, but this was not significant: 1.58 (0.98-2.41), 1.55 (0.67-3.06), 1.78 (0.05-9.93), 1.38 (0.03-7.66), respectively.

The results are consistent with the article published by Gisondi et al. during the peak of the Italian pandemic [3] that suggests that psoriatic patients receiving biologic treatments are not associated with worse outcomes.

A strength of this study is that we analyzed a prospective cohort, that we know the base population and that we can calculate the incidences. This study therefore avoids problems of other ongoing international registries based on case notifications, which do not have a well-defined base population and likely suffer from selection bias [4]. Although the first data were reassuring at the start of the pandemic, some authors consider that it is necessary to confirm them using prospective studies of incidence with adequate denominators [5].

The limitations of this study include the lack of serological or molecular confirmations for the diagnosis of COVID-19 of all possible cases, which is because in cases of mild courses of the disease testing was often not done during the period of the study.

In conclusion, this prospective cohort study suggests that classic systemic or biologic treatments increase neither the susceptibility nor the severity of COVID-19.

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TABLES

Table 1. SARS-CoV-2 infection characteristics of patients treated with systemic therapies.

	SARS-CoV-2 infection						
Characteristics	Possible case, n=36 (%)	Probable case, n=16 (%)	PCR confirmed case, n=21 (%)	Hospitalized case, n=13 (%)	ICU case, n=1 (%)	Death case, n=1 (%)	All cases, n=73 (%)
Sex							
Male	21 (58)	11 (69)	11 (52)	10 (77)	0 (0)	1 (100)	43 (59)
Female	15 (42)	5 (31)	10 (48)	3 (23)	1 (100)	0 (0)	30 (41)
Age (years), median (p25-p75)	51.3 (38.8-59.8)	49.9 (32.7-54.6)	54.8 (49.6-68.3)	54.8 (51.5-68.3)	51.2 (NA)	79.5 (NA)	51.8 (39.6-60.0)
Plaque psoriasis, yes	35 (97)	15 (94)	19 (90)	12 (92)	1 (100)	1 (100)	69 (95)
Psoriatic arthritis, yes	2 (6)	2 (13)	5 (24)	4 (31)	1 (100)	0 (0)	9 (12)
Treatment							
Anti-TNF	6 (16)	5 (31)	2 (10)	1 (8)	0 (0)	0 (0)	13 (18)
Classic Systemics Treatments	3 (9)	2 (12)	4 (19)	2 (15)	0 (0)	0 (0)	9 (12)
Anti-IL-12/IL-23	9 (25)	4 (25)	3 (14)	4 (31)	0 (0)	0 (0)	16 (22)
Anti-IL17	6 (17)	5 (32)	2 (10)	1 (8)	0 (0)	0 (0)	13 (18)
Apremilast	6 (17)	0 (0)	6 (29)	2 (15)	0 (0)	1 (100)	12 (16)
Fumarates	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Anti-IL-23p19	5 (14)	0 (0)	4 (19)	3 (23)	1 (100)	0 (0)	9 (12)
Changes in current treatment							
No	29 (81)	12 (75)	20 (95)	12 (92)	1 (100)	1 (100)	61 (84)
Preventive minimization	3 (8)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)	5 (7)
Preventive suspension	4 (11)	2 (13)	1 (5)	1 (8)	0 (0)	0 (0)	7 (10)
Hypertension, yes	11 (31)	3 (19)	6 (29)	5 (38)	0 (0)	1 (100)	20 (27)
Diabetes mellitus, yes	7 (19)	2 (13)	3 (14)	5 (38)	0 (0)	0 (0)	12 (16)
Cardiovascular disease, yes	6 (17)	2 (13)	4 (19)	4 (31)	0 (0)	1 (100)	12 (16)
Respiratory tract disease, yes*	8 (22)	4 (25)	1 (5)	3 (23)	0 (0)	NA	13 (18)
ARA II or ACE treatments, yes	8 (22)	3 (19)	5 (24)	4 (31)	0 (0)	1 (100)	16 (22)
Relative hospitalized or death by COVID-19*	3 (10)	2 (17)	2 (22)	5 (100)	1 (100)	NA	7 (14)
Time since first symptom, median (p25-p75) *	20.5 (12-26)	23 (15-41)	18 (13.5-30)	23 (13-30)	30 (NA)	14 (NA)	20 (13-30)
COVID-19 outcome							
Mild symptoms or asymptomatic	35 (97)	12 (75)	11 (52)	0 (0)	0 (0)	0 (0)	58 (79)
Hospitalization	1 (3)	4 (25)	8 (38)	13 (100)	0 (0)	0 (0)	13 (18)
ICU admission or similar	0 (0)	0 (0)	1 (5)	0 (0)	1 (100)	0 (0)	1 (1)
Death	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	1 (100)	1 (1)

Possible case: febrile respiratory infection with compatible symptoms; probable case: clinical criteria with an epidemiological link or any person meeting the diagnostic criteria and confirmed case: laboratory confirmation of SARS-CoV-2, irrespective of clinical signs and symptoms. *Few missing data.

Table 2. Adjusted Cumulative Incidence and Standardized Incidence Ratio of psoriatic patients treated with systemic therapies and compared to equivalent definition in the general population of Spain.

	Observed cases in Biobadaderm	Expected cases	Adjusted Cumulative Incidence 95CI% (per 100,000 patient-years)	SIR 95CI%
All PCR confirmed cases vs Spanish confirmed cases	21	13.3	959.5 (593-1469)	1.58 (0.98-2.41)
PCR Hospitalized cases vs Spanish hospitalized cases	8	5.2	349.8 (149.4-692.6)	1.55 (0.67-3.06)
PCR ICU cases vs Spanish ICU cases	1	0.6	33.5 (0-192)	1.78 (0.05-9.93)
PCR death cases vs Spanish death cases	1	0.7	69.5 (0-398.3)	1.38 (0.03-7.66)

PCR: Polymerase Chain Reaction; ICU: Intensive Care Unit; aCI: SIR: Standardized Incidence Ratio; CI: Confidence Intervals

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- 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 Carrascosa has participated as speaker and/or advisor for Celgene, Janssen, Lilly, Novartis, Leo Pharma, Pfizer, MSD, Abbvie, Biogen Amgen.
- 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 Herrera-Acosta has served as consultant and/or speaker with Leo Pharma, Novartis, Janssen, Lilly, Celgene y Abbvie.
- 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.
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- Dr Belinchón acted as a consultant and/or speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Janssen Pharmaceuticals Inc, Almirall SA, Lilly, AbbVie, Novartis, Celgene, Biogen Amgen, Leo-Pharma, UCB, Pfizer-Wyeth, and MSD.
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- Dr Alsina gave expert testimony for Merck-Schering Plough, Pfizer, Janssen, Novartis, Lilly and Abbott, and has participated as speaker for Almirall, Janssen and Gebro Pharma.
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The use of systemic treatments in psoriatic patients during the pandemic has been the subject of extensive debate. In March 2020, we performed a specific study within the cohort of Biobadaderm Registry, a previously described national, multicenter, prospective cohort [1]. Our primary objective was to analyze the incidence of COVID-19 infections and severe outcomes in a cohort of psoriatic patients treated with systemic therapies and to compare it to the general population.

We reviewed all Biobadaderm patient records and contacted the patients when needed. We collected information about current comorbidities related to COVID-19 and COVID-19 outcomes in all active patients of the registry. We used the latest data updated on 6 July 2020. We estimated the age and sex standardized incidence ratio (SIR) defined as the ratio of the observed cases to the expected number of cases according to the Spanish population. The main analysis examined hospitalization, ICU and death in PCR-confirmed patients included in Biobadaderm as compared to PCR-confirmed cases published by the Spanish Ministry of Health [2]. Also 95% CI were calculated for each SIR to compare significance between the Spanish figures and Biobadaderm.

In our study, we found that out of 2329 current active patients with systemic therapy, 73 patients (3.13%) had suffered from COVID-19, 13 patients (0.56%) required hospitalization, 1 patient (0.04%) needed ICU and 1 (0.04%) patient died. Patient characteristics are detailed in Table 1. The profile of COVID-19 cases was similar to that of the population of origin (Biobadaderm) in age and sex [3], but with higher percentages of comorbidities like hypertension (27% vs 22%) or diabetes mellitus (16% vs 11%).

In our main analysis (Table 2), the SIR for COVID-19 infection, hospitalization, ICU and death were slightly higher in psoriatic patients treated with systemic therapies compared to the general population of Spain, but this was not significant: 1.58 (0.98-2.41), 1.55 (0.67-3.06), 1.78 (0.05-9.93), 1.38 (0.03-7.66), respectively.

The results are consistent with the article published by Gisondi et al. during the peak of the Italian pandemic [3] that suggests that psoriatic patients receiving biologic treatments are not associated with worse outcomes.

A strength of this study is that we analyzed a prospective cohort, that we know the base population and that we can calculate the incidences. This study therefore avoids problems of other ongoing international registries based on case notifications, which do not have a well-defined base population and likely suffer from selection bias [4]. Although the first data were reassuring at the start of the pandemic, some authors consider that it is necessary to confirm them using prospective studies of incidence with adequate denominators [5].

The limitations of this study include the lack of serological or molecular confirmations for the diagnosis of COVID-19 of all possible cases, which is because in cases of mild courses of the disease testing was often not done during the period of the study.

In conclusion, this prospective cohort study suggests that classic systemic or biologic treatments increase neither the susceptibility nor the severity of COVID-19.

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TABLES

Table 1. SARS-CoV-2 infection characteristics of patients treated with systemic therapies.

	SARS-CoV-2 infection						
Characteristics	Possible case, n=36 (%)	Probable case, n=16 (%)	PCR confirmed case, n=21 (%)	Hospitalized case, n=13 (%)	ICU case, n=1 (%)	Death case, n=1 (%)	All cases, n=73 (%)
Sex							
Male	21 (58)	11 (69)	11 (52)	10 (77)	0 (0)	1 (100)	43 (59)
Female	15 (42)	5 (31)	10 (48)	3 (23)	1 (100)	0 (0)	30 (41)
Age (years), median (p25-p75)	51.3 (38.8-59.8)	49.9 (32.7-54.6)	54.8 (49.6-68.3)	54.8 (51.5-68.3)	51.2 (NA)	79.5 (NA)	51.8 (39.6-60.0)
Plaque psoriasis, yes	35 (97)	15 (94)	19 (90)	12 (92)	1 (100)	1 (100)	69 (95)
Psoriatic arthritis, yes	2 (6)	2 (13)	5 (24)	4 (31)	1 (100)	0 (0)	9 (12)
Treatment							
Anti-TNF	6 (16)	5 (31)	2 (10)	1 (8)	0 (0)	0 (0)	13 (18)
Classic Systemics Treatments	3 (9)	2 (12)	4 (19)	2 (15)	0 (0)	0 (0)	9 (12)
Anti-IL-12/IL-23	9 (25)	4 (25)	3 (14)	4 (31)	0 (0)	0 (0)	16 (22)
Anti-IL17	6 (17)	5 (32)	2 (10)	1 (8)	0 (0)	0 (0)	13 (18)
Apremilast	6 (17)	0 (0)	6 (29)	2 (15)	0 (0)	1 (100)	12 (16)
Fumarates	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Anti-IL-23p19	5 (14)	0 (0)	4 (19)	3 (23)	1 (100)	0 (0)	9 (12)
Changes in current treatment							
No	29 (81)	12 (75)	20 (95)	12 (92)	1 (100)	1 (100)	61 (84)
Preventive minimization	3 (8)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)	5 (7)
Preventive suspension	4 (11)	2 (13)	1 (5)	1 (8)	0 (0)	0 (0)	7 (10)
Hypertension, yes	11 (31)	3 (19)	6 (29)	5 (38)	0 (0)	1 (100)	20 (27)
Diabetes mellitus, yes	7 (19)	2 (13)	3 (14)	5 (38)	0 (0)	0 (0)	12 (16)
Cardiovascular disease, yes	6 (17)	2 (13)	4 (19)	4 (31)	0 (0)	1 (100)	12 (16)
Respiratory tract disease, yes*	8 (22)	4 (25)	1 (5)	3 (23)	0 (0)	NA	13 (18)
ARA II or ACE treatments, yes	8 (22)	3 (19)	5 (24)	4 (31)	0 (0)	1 (100)	16 (22)
Relative hospitalized or death by COVID-19*	3 (10)	2 (17)	2 (22)	5 (100)	1 (100)	NA	7 (14)
Time since first symptom, median (p25-p75) *	20.5 (12-26)	23 (15-41)	18 (13.5-30)	23 (13-30)	30 (NA)	14 (NA)	20 (13-30)
COVID-19 outcome							
Mild symptoms or asymptomatic	35 (97)	12 (75)	11 (52)	0 (0)	0 (0)	0 (0)	58 (79)
Hospitalization	1 (3)	4 (25)	8 (38)	13 (100)	0 (0)	0 (0)	13 (18)
ICU admission or similar	0 (0)	0 (0)	1 (5)	0 (0)	1 (100)	0 (0)	1 (1)
Death	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	1 (100)	1 (1)

Possible case: febrile respiratory infection with compatible symptoms; probable case: clinical criteria with an epidemiological link or any person meeting the diagnostic criteria and confirmed case: laboratory confirmation of SARS-CoV-2, irrespective of clinical signs and symptoms. *Few missing data.

Table 2. Adjusted Cumulative Incidence and Standardized Incidence Ratio of psoriatic patients treated with systemic therapies and compared to equivalent definition in the general population of Spain.

	Observed cases in Biobadaderm	Expected cases	Adjusted Cumulative Incidence 95CI% (per 100,000 patient-years)	SIR 95CI%
All PCR confirmed cases vs Spanish confirmed cases	21	13.3	959.5 (593-1469)	1.58 (0.98-2.41)
PCR Hospitalized cases vs Spanish hospitalized cases	8	5.2	349.8 (149.4-692.6)	1.55 (0.67-3.06)
PCR ICU cases vs Spanish ICU cases	1	0.6	33.5 (0-192)	1.78 (0.05-9.93)
PCR death cases vs Spanish death cases	1	0.7	69.5 (0-398.3)	1.38 (0.03-7.66)

PCR: Polymerase Chain Reaction; ICU: Intensive Care Unit; aCI: SIR: Standardized Incidence Ratio; CI: Confidence Intervals

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