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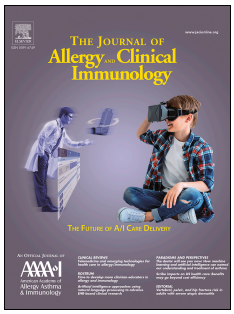

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Incidence rates of hospitalization and death from COVID-19 in patients with psoriasis receiving biological treatment: a Northern Italy experience

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Declaration of interest

- Paolo Gisondi has been a consultant and/or speaker for Abbvie, Almirall, Celgene, Janssen, Leo-pharma, Eli Lilly, Novartis, Pfizer, Sandoz, UCB;
- Stefano Piaserico has been a consultant and/or speaker for Abbvie, Almirall, Celgene, Janssen, Leo-pharma, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Sandoz, UCB;
- Luigi Naldi has been a consultant and/or speaker for Abbvie, Almirall, Celgene, Janssen, Eli Lilly, Novartis;
- Paolo Dapavo has been a consultant and/or speaker for Abbvie, Celgene, Leo-pharma, Eli Lilly, Novartis, UCB;
- Andrea Conti has been a consultant and/or speaker for Abbvie, Almirall, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, UCB;
- Piergiorgio Malagoli has been a consultant and/or speaker for Abbvie, Almirall, Celgene, Genzyme, Janssen, Leo-pharma, Eli Lilly, Novartis, Sanofi, UCB, Pierre Fabre;
- Federico Bardazzi has been a consultant and/or speaker for Abbvie, Almirall, Celgene, Janssen, Leo-pharma, Eli Lilly, Novartis, Pfizer, Sandoz, UCB
- Massimo Gasperini has nothing to declare
- Simone Cazzaniga has nothing to declare
- Antonio Costanzo has been a consultant and/or speaker for Abbvie, Almirall, Celgene, Janssen, Leo-pharma, Eli Lilly, Novartis, Pfizer, Sandoz, UCB.

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Abstract

Introduction: Whether biologic therapies enhance the risk of COVID-19 or affect the disease outcome in patients with chronic plaque psoriasis remains to be ascertained.

Objective: investigating the incidence of hospitalization and death for COVID-19 in a large sample of patients with plaque psoriasis receiving biologic therapies compared with the general population.

Materials and methods: This is a retrospective multicenter cohort study including patients with chronic plaque psoriasis (n=6,501) being treated with biologic therapy and regularly followed up at the Divisions of Dermatology of several main hospitals in the Northern Italian cities of Verona, Padua, Vicenza, Modena, Bologna, Piacenza, Turin, and Milan. Incidence rates (IR) of hospitalization and death per 10,000 person-months with exact mid-p 95% confidence intervals (CI) and standardized incidence ratios (SIR) were estimated in the psoriasis patients and compared with the general population in the same geographic areas.

Results: The IR of hospitalization for COVID-19 was 11.7 (95% CI: 7.2-18.1) per 10,000 person-months in psoriasis patients and 14.4 (95% CI: 14.3-14.5) in the general population; the IR of death from COVID-19 was 1.3 (95% CI: 0.2-4.3) and 4.7 (95% CI: 4.6-4.7) in psoriasis patients and the general population, respectively. The SIR of hospitalization and death in psoriasis patients compared with the general population was 0.94 (95% CI: 0.57-1.45; p=0.82) and 0.42 (95% CI: 0.07-1.38; p=0.19) respectively.

Conclusions: Our data did not show any adverse impact of biologics on COVID-19 outcome in psoriasis patients. We would not advise biologic discontinuation in patients on treatment since more than 6 months and not infected with SARS-CoV-2 to prevent hospitalization and death from COVID-19.

Key Messages: Biologic discontinuation in psoriasis patients on treatment to prevent hospitalization and death from COVID-19 is not advisable, unless they are infected with SARS-CoV-2.

Key words: psoriasis, biologics, COVID-19, interstitial pneumonia

Abbreviations: SARS-CoV-2, the severe acute respiratory syndrome coronavirus 2; TNF-α,Tumor Necrosis Factor-α; IL, interleukin; PASI, psoriasis area and severity index;

ISTAT, Istituto Nazionale di Statistica; SD, standard deviation; IR, incidence rate; CI, confidence intervals; SIR, standardized incidence ratios; IBD, inflammatory bowel disease; PsA, psoriatic arthritis;

Capsule Summary

There is no evidence for an increased risk of hospitalization or death from COVID-19 in psoriatic patients compared with general population, although they are treated with biologics and affected by cardiometabolic comorbidities.

Introduction

Italy has been deeply affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic particularly in the northern regions (1). There is substantial concern among physicians regarding an increased risk of COVID-19 in patients who are being treated with biologic therapies (2). However, whether biologics enhance this risk and/or if the disease course is worsened by the immunosuppressive/immunomodulating treatment remains to be determined. It is debated whether biologics for psoriasis should be interrupted for preventing severe complications of SARS-CoV-2 infection such as interstitial pneumonia. Notably, SARS-CoV-2 infection seems to be most fatal when it triggers a cytokine storm, including Tumor Necrosis Factor (TNF)-α, interleukin (IL)-6 and IL-17 (3-4). Therefore, biologics are being investigated as treatments for COVID-19 (5).

In this study, we evaluated the incidence of hospitalization and death for COVID-19 in a large sample of patients with plaque psoriasis receiving biologic therapies compared with the general population.

Results/Discussion

The characteristics of the studied population are reported in the Table. The prevalence of male gender and comorbidities (obesity, arterial hypertension and diabetes) were significantly higher in psoriasis patients than in the general population. We estimated the IR of hospitalization and death for COVID-19 in 6,501 patients with plaque psoriasis receiving biologic therapies, corresponding to 15,378.5 patient-months of follow-up, and compared the figures with those obtained from the general adult population of Northern Italy corresponding to 19,978,806 subjects and 47,260,897.6 patient-months of follow-up. The IR of hospitalization for COVID-19 was 11.7 (95% CI: 7.2-18.1) per 10,000 person-months in psoriasis patients and 14.4 (95% CI: 14.3-14.5) in the general population; the IR of death from COVID-19 was 1.3 (95% CI: 0.2-4.3) and 4.7 (95% CI: 4.6-4.7) in psoriasis patients and the general population, respectively. The SIR of hospitalization and death in psoriasis patients compared with the general population was 0.94 (95% CI: 0.57-1.45; p=0.82) and 0.42 (95% CI: 0.07-1.38; p=0.19) respectively. We found no significant difference in the rates of hospitalization with the general population when stratifying by age (<65 vs. ≥65 years) or by class of biologic (Table). There were no further deaths for other causes during the study period. We had 1,865 out of 6,501 (i.e. 28.7%) patients affected by PsA. Four out of 18 hospitalized psoriasis patients had PsA, whereas none of the dead ones had PsA. All the hospitalized patients fully recovered from the viral infection and then re-started biologic therapy because of psoriasis relapse after a period of time ranging from 6 to 15 weeks from the hospital discharge. They are currently on biologic.

The major finding of our study is that, although psoriatic patients treated by biologics are burdened by higher rates of metabolic and cardiovascular comorbidities, there was no evidence for an increased risk of hospitalization or death from COVID-19 in those patients compared with the general population. Accordingly, some preliminary data on TNF-- α inhibitors and IL12/23 inhibitors in inflammatory bowel disease (IBD) patients

showed that these therapies do not worsen the clinical course of COVID-19 compared with sulfasalazine/mesalamine or no treatment (9). On the opposite, biologics appeared to be associated with a better outcome, even though there were insufficient data to make definite statements (10). Some systemic complications caused by SARS-CoV-2 infection appear to be associated with excessive inflammatory and cytokine responses (3). Therefore, treatments that reduce the host inflammatory response, including agents blocking TNF-α, IL-6 or IL-17 pathways, in combination with therapies that have direct anti-viral activity, have been proposed, and are currently under investigation for the treatment of COVID-19 (11-13).

We acknowledge the limitations of our study, including the absence of serological or molecular investigations for the diagnosis of SARS-CoV-2 infection in asymptomatic patients with psoriasis. The objective of our study was not to investigate the prevalence of the SARS-CoV-2 infection, but to report the occurrence of hospitalization and death, as indicators of severe outcomes related to COVID-19. Despite a cohort of 6,501 psoriatic patients receiving biologic treatment, we collected relatively few COVID-19 cases, with wide CIs. The low rates in patients treated with biologics are reassuring, especially considering that these patients had a high prevalence of comorbidities that are usually associated with a worse COVID-19 course. Despite a great effort has been made in retrieving COVID-19 patients, we acknowledge that there is still a possibility that we have missed important cases. However, based on a simulation analysis on our sample size, we estimated that around 3 missed deaths would be required to observe a SIR=1 and at least 8 deaths for a SIR>2 with p-value<0.05. On the other hand, we would have missed at least 11 hospitalized patients to observe a SIR>1.5 with p-value<0.05. Therefore, it is unlikely that we have missed a number of patients needed to completely change our results.

There weren't new patients starting biological treatment from February 20th to May 1st in our Divisions of Dermatology. This is because this time period was overlapping with the lockdown imposed by the Italian Government. During that period, public health measures required citizen to stay at home and shield. The clinical dermatological activity was significantly reduced and mostly dedicated to teleconsultation for those patients already on treatment (14). The access to the hospitals was limited only to symptomatic patients with fever, suspected for Sars-Cov-2 infection. The major strengths of our study are the cohort study design, the focus on Italian regions most affected by the SARS-CoV-2 pandemic, and the completeness of the database. We acknowledge that patients on biologic drugs may have self-isolated more efficiently, thus limiting their own infectious risk. We can rule out that there have been deaths at home that we are not aware of and/or that patients have gone to hospitals outside their catchment area. Our findings are consistent with those of another study which reported that patients with psoriasis on biologics were not at an increased risk of Intensive Care Unit admission or death; conversely, the study found that patients were at a higher risk for testing positive for SARS-CoV-2, to be self-quarantined at home or hospitalized (15).

In conclusion, the results of our study show that the continuation of biologic therapies during the pandemic does not influence the development of severe complications of the SARS-CoV-2 infection. A prophylactic treatment discontinuation in an attempt to prevent a negative outcome of COVID-19 may not be required (16). Larger studies with longer follow-up periods are needed to confirm these findings.

For detailed methods, please see the Methods section in this article's Online Repository at www.jacionline.org

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Table. Number of patients with chronic plaque psoriasis being treated with biologic therapy or subjects of the general population of Veneto, Lombardy, Emilia Romagna and Piedmont hospitalized or died for COVID-19 from 20th February to 1st May 2020

Parameter, n (%)	Psoriasis Patients	General population (18+ years)	SIR (95% CI)	P-value^
Number (patient-months)	6,501 (15,378.5)	19,978,806 (47,260,897.6)	-	-
Outcome measure				
Subjects positive for SARS-CoV-2 (IR, 95% CI)	*	144,909 (30.7, 30.5-30.8)	-	-
Hospitalized for COVID-19 (IR, 95% CI)	18 (11.7, 7.2-18.1)	68,099 (14.4, 14.3-14.5)	0.94 (0.57-1.45)	0.82
Deaths for COVID-19 (IR, 95% CI)	2 (1.3, 0.2-4.3)	22,013 (4.7, 4.6-4.7)	0.42 (0.07-1.38)	0.19
Demography				
Male gender	3,616 (55.6%)	9,649,834 (48.3%)	-	<0.001
Age, mean ± SD	53.4 ± 11.0	52.3 ± 20.0	-	<0.001
<65	5,071 (78.0%)	14,403,251 (72.1%)	0.68 (0.30-1.35)°	0.31
≥65	1,430 (22.0%)	5,575,555 (27.9%)	1.06 (0.56-1.85)°	0.80
Comorbidity				
Obesity	1,633 (25.1%)	2,081,748 (10.4%)	-	<0.001
Hypertension	2,012 (30.9%)	4,261,658 (21.3%)	-	<0.001
Diabetes mellitus	854 (13.1%)	1,124,563 (5.6%)	-	<0.001
Psoriatic arthritis	1,865 (28.7%)	-	-	-
Biologic Therapy				
TNF-α inhibitors	2,106 (32.4%)	-	1.02 (0.41-2.12)°	0.91
IL-17 inhibitors	2,486 (38.2%)	-	0.80 (0.32-1.67)°	0.62
IL-12/23 inhibitor	1,691 (26.0%)	-	0.98 (0.36-2.17)°	1
IL-23 inhibitors	218 (3.3%)	-	1.45 (0.07-7.16)°	0.65

Legend: CI: confidence interval, GP: general population; IR: incidence rate x 10,000 person-months; SIR: standardized incidence ratio

* Asymptomatic individuals were not tested so the true number of COVID-19 positive patients is unknown.

^ Exact mid-p test was reported for SIR. Pearson's X^2 test and two-sample t-test were used for the comparison of nominal and continuous variables between groups.

° SIR for COVID-19 hospitalization was reported.

Data of subjects hospitalized or died for COVID-19 in the general population are from the civil protection official repository (https://github.com/pcm-dpc/COVID-19) and from the National Health Institute (ISS) (https://www.epicentro.iss.it/coronavirus/), last accessed on May 1, 2020.

Data of patients with psoriasis hospitalized or died for COVID-19 are from electronic medical records of the participating Hospitals, last accessed on May 1, 2020.

Data of comorbidities in the general population are from ISTAT multipurpose survey 2019 (https://www.istat.it/it/files/2019/12/Asi-2019.pdf), last accessed on May 1, 2020.

Materials and Methods

This is a retrospective multicenter cohort study of patients with chronic plaque psoriasis (n=6,501) treated with biologic therapy at a large number of hospitals in Northern Italy. Incidence rates of hospitalization or death from COVID-19 were assessed in these patients and compared with data from the general population in the same geographic areas between February 20th and May 1st, 2020. Inclusion criteria for psoriatic patients were: being regularly followed up at the Divisions of Dermatology of the hospitals of Verona, Padua, Vicenza, Modena, Bologna, Piacenza, Turin, Milan (Humanitas hospital, San Donato hospital, Ca' Granda Ospedale Maggiore Policlinico); being currently treated with a biological agent, including TNF-α, IL-17, IL-12/23 or IL-23 inhibitors; the minimal length of treatment required for inclusion in the study was 6 months. Clinical data, including comorbidities, were obtained by consulting the electronic medical records of each hospital, and/or by directly contacting the patients either by visit, phone or email. In particular, case ascertainment (i.e. being hospitalized or dead) was confirmed by contacting, either by phone or by telecommunications application providing video chat and voice (e.g. Skype), all the psoriasis patients included in the study. For study purposes, demographic data and data on comorbidities in the general adult population of the Italian Regions of Veneto, Emilia Romagna, Piedmont and Lombardy were retrieved from the Istituto Nazionale di Statistica (ISTAT) census data (and the ISTAT multipurpose survey 2019 (6-7). Data on adult COVID-19 confirmed cases, including demographics, hospitalizations and deaths, were extracted from the civil protection official repository (https://github.com/pcm-dpc/COVID-19) and from the National Health Institute (ISS) (8).

Statistical analysis

For descriptive purposes data were presented as means with standard deviations (SD) or numbers with percentages for continuous and categorical variables respectively. Incidence rates (IR) were calculated as the number of observed cases per 10,000 person-months

with exact mid-p 95% confidence intervals (CI). For comparison purpose, standardized incidence ratios (SIR) were calculated by using indirectly standardized rates from the number of observed events in the study population and the number of expected events derived by applying, to the target population, age, gender and regional specific rates of the general adult population of the same geographical areas during the same period of time. SIR were reported along with their exact mid-p 95% CI and p-values. A stratified SIR analysis by age and class of biologic was also performed for COVID-19 hospitalization. Differences in the distribution of demographics and comorbidities between groups were assessed by using Pearson's X^2 test and two-sample t-test for nominal and continuous variables respectively. All tests were considered significant at p-value <0.05. Analyses were carried out with R software v.3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).