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Risk of COVID-19 Infection, Hospitalization, and Mortality in Patients with Psoriasis Treated by Interleukin-17 Inhibitors

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Running head: IL-17 inhibitors during COVID-19 pandemic

Keywords: Psoriasis; IL-17 inhibitors; COVID-19; Biologics

Abstract

Background: The risk of the infection and its complications under this drug class remains to be determined.

Objective: To evaluate the risk of COVID-19, COVID-19-associated hospitalization, and mortality among patients with psoriasis treated by IL-17I.

Methods: A population-based cohort study was performed to compare psoriasis patients treated by IL-17I (n=680) with those treated by methotrexate (n=2,153) and non-systemic/non-immunomodulatory treatments (n=138,750) regarding the incidence of COVID-19 and its complications.

Results: The use of IL-17I was not associated with an increased risk of COVID-19 infection [adjusted HR for IL-17I vs. methotrexate: 0.91 (95% CI, 0.48-1.72); IL-17I vs. non-systemic/non-immunomodulatory treatments: 0.92 (95% CI, 0.54-1.59)]. IL-17I was associated with comparable risk of COVID-19-associated hospitalization [adjusted HR for IL-17I vs. methotrexate: 0.42 (95% CI, 0.05-3.39); IL-17I vs. non-systemic/non-immunomodulatory treatments: 0.65 (95% CI, 0.09-4.59)] and COVID-19-associated mortality [adjusted HR for IL-17I vs. methotrexate: 7.57 (95% CI, 0.36-157.36); IL-17I vs. non-systemic/non-immunomodulatory treatments: 7.05 (95% CI, 0.96-51.98)]. In a sensitivity analysis, neither secukinumab nor ixekizumab imposed an elevated risk of any of the outcomes of interests.

Conclusions: IL-17I treatment does not confer an increased risk of COVID-19 infection or its complications in patients with psoriasis. Our findings support the continuation of IL-17I treatment during the pandemic.

Introduction

The introduction of biologic drugs led to a prominent breakthrough in the management of psoriasis. These highly targeted and effective therapies revolutionized the perspective of psoriasis treatment from improving the disease to clearing it(1,2). With these drugs, psoriasis area severity index (PASI) 90 and 100, representing 90% and 100% reduction in PASI, have become the realistic gold standard endpoint measurements in randomized controlled trials (RCT), thus replacing PASI 75 which dominated throughout the decades preceding the biologics` era. While the efficacy of biologics in psoriasis is indisputable, the susceptibility to infections under these drugs has long been a scope of concern(3).

Interleukin (IL) 17 inhibitor (IL-17I) emerged as a promising therapeutic option in psoriasis guaranteeing high efficacy, long-term maintenance of treatment response, and quick onset of action(4–6). IL-17 cytokine exerts a crucial role in the maintenance of tissue integrity and the generation of protective immune responses against infectious microorganisms, particularly at epithelial barrier sites(7). IL-17 deficiency models displayed an increased risk of bacterial, fungal, and viral infections(8,9). The role of IL-17 in host defense against pathogens raised concerns about the risk of infections under IL-17I. Overall, IL-17I and IL-17 receptor inhibitors boast an impressive safety profile despite an elevated risk of mucocutaneous candidiasis(10) and respiratory tract infections(11). The risk of coronavirus disease 2019 (COVID-19) and its complications among patients with psoriasis under IL-17I remains to be determined.

The medical community struggles with major uncertainty regarding the optimal way to manage patients with immune-mediated diseases necessitating systemic drugs during the COVID-19 pandemic. Since immunosuppressive and immunomodulatory therapy might interfere with antiviral immunity(12), patients under these medications, particularly those with severe comorbidities, might be more vulnerable to worse outcomes of COVID-19. Inversely, it has been postulated that over-activation of the immune system underlies the lung injury caused by SARS-CoV-2 and that a subgroup of patients might benefit

from immunosuppressive drugs(13). The burden of COVID-19 and predictors of its complications among patients with psoriasis are yet to be delineated.

The objective of the current study is to evaluate the risk of COVID-19 and COVID-19-associated hospitalization and mortality among patients with psoriasis treated by IL-17I (secukinumab and ixekizumab). To precisely investigate the safety of this treatment during the pandemic, patients under IL-17I were compared with two reference groups: (i) psoriasis patients treated by methotrexate and (ii) non-systemic/non-immunomodulatory treatments.

Methods

Study design and dataset

The current study was designed as a historical retrospective cohort study that followed patients with psoriasis treated by IL-17I, methotrexate, and non-systemic agents to evaluate the incidence of COVID-19, COVID-associated hospitalization, and mortality. The study was approved by the institutional review board (IRB) of Ben-Gurion University in accordance with the declaration of Helsinki (approval code: 0212-17-COM).

The electronic database of Clalit Health Services (CHS) was the source of the current study. CHS is the largest healthcare maintenance organization in Israel, which covers a broad assortment of private and public healthcare services for 4,540,768 enrollees as of October 2018. The inclusiveness of CHS dataset stems from its ability to retrieve data from numerous sources covering both primary care and referral center settings and both ambulatory and hospitalized care settings. Additional distinct traits of CHS lie in the negligible loss to follow-up and free access to healthcare services. The latter renders this dataset highly compatible with the performance of reliable and well-designed epidemiological studies(14).

Study population and definition of exposure and analyses

The computerized dataset of CHS was systematically screened for all prevalent cases with a diagnostic code of psoriasis as registered by a board-certified dermatologist or as documented in the discharge letter of patients admitted to dermatological wards. Eligible patients were alive and active members of CHS at the onset of the pandemic, defined as the date of the first confirmed case of COVID-19 in Israel (February 27th, 2020).

Exposure to all drugs was defined in case the drug was prescribed for at least one month during the pandemic. For the main analysis, patients with psoriasis receiving IL-17I were compared to those

receiving methotrexate as a reference group. Patients treated by IL-17I or methotrexate in conjunction with other concomitant systemic agents were omitted from the analysis to enable to more precisely estimate the independent role exerted by the drugs of interest.

A sensitivity analysis was performed to evaluate the risk of COVID-19 in patients treated by the two available IL-17I agents in Israel; secukinumab and ixekizumab. Each of these drugs was separately compared to methotrexate. Numerous patients were exposed both to secukinumab and ixekizumab during the pandemic. The time under each of the drugs was considered separately in the respective sensitivity analysis, whereas the cumulative time under both of them was calculated in the main analysis.

The secondary analysis compared patients with IL-17I with those with non-systemic/non-immunomodulatory treatments as a reference group. The latter group encompasses untreated patients or patients treated by topical treatments, phototherapy, Dead Sea climate therapy, or acitretin.

Definition of COVID-19-related outcomes

The medical records of eligible patients were checked for a diagnosis of COVID-19. The diagnosis of COVID-19 relied on confirmation of cases by a US Food and Drug Administration (FDA)-approved molecular tests. COVID-19-associated hospitalization was defined in COVID-19-confirmed patients admitted to intensive care units, internal medicine, or COVID-19-specific respiratory inpatient wards. COVID-19-associated mortality was defined in COVID-19-confirmed patients whose cause of death was ascribed to COVID-19 or its complications.

Study participants` date of death was ascertained by linking the study cohort with the National Registry of Deaths Database. All study participants were followed up from the onset of the pandemic in Israel until October 2^{nd,} 2020, or death, whichever occurs earlier.

Covariates

Outcome measures were adjusted for underlying comorbidities as assessed by the Charlson comorbidity index (CCI), a validated epidemiological method to quantify comorbidities. This index has been found to be reliable in predicting mortality and is widely utilized in epidemiological studies(15). Among others, CCI include diabetes mellitus, respiratory and cardiovascular diseases, all of which were evidenced to confer worse outcomes in COVID-19(16). COVID-19 outcomes were additionally adjusted for smoking owing to the association of the latter with worse outcomes of COVID-19(16,17).

Statistical analysis

Baseline characteristics were described by means and standard deviations (SD)s for continuous variables and percentages for categorical variables. Continuous variables were compared using analysis of variance (ANOVA) and the non-parametric Kruskal-Wallis H test (based on the homogeneity of variance in each comparison as determined by Levene`s test). Dichotomous variables were compared by Pearson chi-square.

Incidence rates of outcomes were calculated and expressed as the number of events per 1,000 person-years. Hazard ratios (HR)s for the risk of incident outcomes were obtained by the use of the Cox regression model. Two-tailed P-values less than 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS software, version 25 (SPSS, Armonk, NY: IBM Corp).

Results

The current study encompassed 680, 2,153, and 138,750 patients treated by IL-17I, methotrexate, and non-systemic/non-immunomodulatory drugs at the onset of the pandemic, respectively. Compared to those treated by methotrexate, patients treated by IL-17I were younger at the onset of the pandemic, had a more prominent male and Jewish preponderance, a higher prevalence of smoking, but a lower prevalence of COPD, diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, and malignancy. The baseline characteristics of study participants are detailed in ***Table 1***.

The risk of COVID-19 and its complications among patients treated by IL-17I relative to those treated by methotrexate

The incidence rate of COVID-19, COVID-19-associated hospitalization, and COVID-19-associated mortality in the IL-17I group was estimated at 31.6 (95% CI, 17.6-52.7), 2.4 (95% CI, 0.1-12.0), and 2.4 (0.1-11.9) per 1,000 person-years, respectively. The corresponding incidence rates in the methotrexate group were 32.3 (95% CI, 23.6-43.3), 8.4 (95% CI, 4.4-14.7), and 0.8 (95% CI, 0.1-3.8) per 1,000 person-years, respectively (***Table 2***).

The multivariate risk of COVID-19 infection (fully adjusted HR, 0.91; 95% CI, 0.48-1.72; P=0.779), COVID-19-associated hospitalization (fully adjusted HR, 0.42; 95% CI, 0.05-3.39; P=0.413) and mortality (fully adjusted HR, 7.57; 95% CI, 0.36-157.36; P=0.191) was comparable between patients treated by IL-17I and methotrexate. The statistically similar risk between the groups persisted in a sex-stratified analysis (***Table 2***).

In a sensitivity analysis, we estimated the risk of the aforementioned outcomes in patients treated by secukinumab (n=451; ***Supplementary Table 1***) and ixekizumab (n=249; ***Supplementary Table 2)*** relative to psoriasis patients treated by methotrexate. The risk of COVID-19 infection, COVID-19-associated hospitalization, and mortality were not increased both in the secukinumab and ixekizumab. Of note, 20 patients were treated by both agents since the onset of the pandemic.

The risk of COVID-19 and its complications among patients treated by IL-17I relative to those treated by non-systemic/non-immunomodulatory treatments

The incidence rate of COVID-19, COVID-19-associated hospitalization, and mortality in the non-systemic/non-immunomodulatory group was estimated at 36.3 (95% CI, 35.0-37.6), 8.4 (95% CI, 4.4-14.7), and 0.6 (0.4-0.8) per 1,000 person-years, respectively (***Table 3***).

The risk of acquiring COVID (fully adjusted HR, 0.92; 95% CI, 0.54-1.59; P=0.776), being hospitalized (fully-adjusted HR, 0.65; 95% CI, 0.09-4.59; P=0.662) and dying due to the infection (fully-adjusted HR, 7.05; 95% CI, 0.96-51.98; P=0.055) was comparable between psoriasis patients treated by IL-17I and non-systemic/non-immunomodulatory treatments (***Table 3***). In a sex-stratified analysis, female patients treated by IL-17I demonstrated an increased risk of COVID-19-associated mortality relative to those treated by non-systemic drugs (HR, 11.22; 95% CI, 1.51-83.62; P=0.018; Table 3). ***Figure 1*** summarizes the main findings of the current study.

Discussion

The current large-scale population-based cohort study is the first of its kind to estimate the risk of COVID-19 and its complications among patients with psoriasis treated by IL-17I. We found a comparable risk of COVID-19 infection, COVID-19-associated hospitalization, and mortality in patients under IL-17I as compared both to those under methotrexate and non-systemic/non-immunomodulatory treatments. This finding persisted in a sensitivity analysis stratifying by secukinumab and ixekizumab.

The general role of immunomodulatory drugs in COVID-19

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), imposes an unprecedented global health crisis with vast social, mental, and financial ramifications(18). This pandemic confronted the medical society with a wide array of unanswered questions regarding the safety of immunosuppressive and immunomodulatory agents during the pandemic. The current literature encompasses an inconsistent body of evidence regarding the outcomes of COVID-19 under these medications among patients with immune-related and inflammatory diseases. These inconsistent observations may actually mirror the differential role exerted by immunosuppressive agents throughout different stages of the triphasic course of COVID-19(12). In the initial phase of the disease, when the host immune response is essential to constrain viral replication, immunosuppressive and immunomodulatory drugs might be disadvantageous(19). However, these drugs may impart a protective effect in the advanced severe phase of the diseases, when an overshoot of the host immune response (the “cytokine storm”), also referred to as secondary hemophagocytic lymphohistiocytosis, can result in acute respiratory distress syndrome (ARDS), multi-organ failure, and mortality(12).

The role of IL-17 and IL-17I in COVID-19

IL-17 was discovered in the 1990s and has since risen as a pleiotropic cytokine that contributes in unique ways to the host immune response. This multifunctional cytokine was found to lend a hand to a variety of physiological and pathophysiological processes, including maintenance of tissue integrity,

progression of cancer, and development of immune-mediated disease(20). Of interest, IL-17 exerts a bidirectional role in the regulation of viral infections. While it takes a crucial part in host defense mechanisms, it has also been implicated, under certain circumstances, in the promotion of viral infection and related illness(20). The predominant role of IL-17 seems to be reliant on (i) the tissue in which this cytokine is expressed and (ii) the trigger of IL-17 secretion. These two factors determine whether the prevailing effect of its expression is protective or whether it drives a detrimental hyper-inflammatory state(9,21,22).

Acute respiratory distress syndrome (ARDS) develops in 81% of fatal cases with COVID-19(23). In ARDS, IL-17 was found to boost the destruction of lung parenchyma by stimulating pro-inflammatory mediators, by maladaptive neutrophil recruitment, and by inhibiting apoptosis through increasing granulocyte colony-stimulating factor expression(24). Correspondingly, a recent genetic study revealed two functional polymorphisms of IL-17, which were associated with ARDS severity and prognosis(25). Patients with a polymorphism leading to attenuated IL-17 production demonstrated an increased 30-day survival, whilst a polymorphism leading to increased IL-17 levels associated with reduced survival(25). Additionally, viral myocarditis in the setting of ARDS contributes to COVID-19-associated mortality(26). IL-17, among a characteristic T helper (TH) 17 type-dominant milieu, has been found to drive more severe viral myocarditis(27). Aligning with the aforementioned observations, the severity of COVID-19 was found to positively correlate with levels of IL-17 and other TH17 cell-related pro-inflammatory cytokines, such as IL-1, IL-6, IL-15, interferon (IFN) γ, and TNF(28). These findings led several authors to postulate that the utilization of IL-17I in patients with severe COVID-19 may be of benefit(22,29).

Since their introduction a few years ago, IL-17Is demonstrated a favorable safety profile(30). All the three FDA-approved agents for psoriasis: secukinumab (human monoclonal antibody to IL-17), ixekizumab (humanized monoclonal antibody to IL-17), and brodalumab (human monoclonal antibody to the IL-17 receptor) are supplied with warnings about increased susceptibility to infections. The risk of upper respiratory infections (URI) was among the most frequent infectious conditions detected in RCTs.

Relative to placebo, secukinumab displayed a moderate increase in the risk of URI(4), whereas a comparable and lower risk of URIs were evidenced in patients treated with ixekizumab and brodalumab, respectively(5,31). These reassuring findings were validated in subsequent studies taking advantage of longer follow-up durations and post-marketing surveillance data(32,33). While the occurrence of COVID-19 infection among patients treated by IL-17I was reported(34–37), a population-based estimate of the disease burden and complications is yet to be investigated. In a tertiary center in Italy, 119 patients were under secukinumab at the beginning of the national lockdown, none of whom developed COVID-19 or discontinued the treatment(38).

Implications of the current study

The current study provides a novel insight regarding the real-life safety of IL-17I during the COVID-19 pandemic. Patients under these drugs did not experience an increased risk of the infection or its complications. The latter accords with the safety profile of biologics during the pandemic among patients with inflammatory bowel disease(39,40) and rheumatic diseases(41). Our findings, once authenticated in additional studies originating from different regions, may lend weight to the approach suggesting to avoid preventively discontinuing effective biologic medications(42). However, patients under biologics may be monitored individually, with all clinical decisions taken on the basis of the individual patient risk factors and comorbid conditions. Strictly following social distancing, standard respiratory hygiene, regular hand washing, and carefulness to avoid sick contacts may be of great importance for these patients, even more than the general population(43).

Strengths and limitations

Apart from its novelty, the large sample size and the various analyses represent a considerable strength of the current study. The allocation of two reference groups enables an assessment of the relative risk of COVID-19 in patients with psoriasis under IL-17I relative to those treated with other agents. Since CHS dataset facilitates inclusive access to the whole spectrum of healthcare services, it is highly

compatible with detecting COVID-19 cases, even those occurring years following the initial diagnosis of psoriasis, thus overcoming loss to follow which frequently hinders hospital-based studies. The study was undertaken in a country typified by a high incidence of COVID-19, thus allowing the detection and characterization of COVID-19-positive psoriasis patients. Limitations that should be acknowledged stems from the small number of outcome events (COVID-19 associated hospitalization and mortality) as well as the relatively short duration of follow-up.

In conclusion, the current population-based study found no increased risk of COVID-19 infection, COVID-19-associated hospitalization, and mortality among patients with psoriasis treated by IL-17I. This finding holds true when comparing IL-17I both to methotrexate and non-systemic/non-immunomodulatory agents as well as in a sensitivity analysis stratifying by the two available IL-17I agents in the country (secukinumab and ixekizumab). These findings lend credibility to the approach advocating to avoid preventive cessation of IL-17I management unless indicated individually by the patient clinical data, comorbidities, or specific risk factors.

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Table 1: Baseline characteristics of the study population

Characteristic	**IL-17 inhibitors (N=680)**	**Methotrexate (N=2,153)**	**Non-systemic or non-immunomodulatory treatment[a] (N=138,750)**	**P value**
Age at the onset of pandemic, years				
Mean (SD)	52.2 (14.9)	58.3 (17.4)	50.1 (20.5)	**<0.001**
Age at the onset of the disease, years				
Mean (SD)	41.7 (14.9)	49.3 (16.8)	42.3 (20.1)	**<0.001**
Sex, n (%)				
Male	364 (53.5%)	1,030 (47.8%)	67,559 (48.7%)	
Female	316 (46.5%)	1,123 (52.2%)	71,191 (51.3%)	**0.030**
Ethnicity, n (%)				
Jews	584 (85.9%)	1,751 (81.3%)	115.854 (83.5%)	**0.006**
Arabs	96 (14.1%)	402 (18.7%)	22,896 (16.5%)	
BMI, mg/kg^2				
Mean (SD)				
Smoking, n (%)	377 (55.4%)	979 (45.5%)	54,668 (39.4%)	**<0.001**
COPD, n(%)	23 (3.4%)	115 (5.3%)	4,710 (3.4%)	**<0.001**
Diabetes mellitus, n (%)	177 (26.0%)	603 (28.0%)	24,593 (17.7%)	**<0.001**
Hypertension, n (%)	203 (29.9%)	825 (38.3%)	36,677 (26.4%)	**<0.001**
Hyperlipidemia, n (%)	375 (55.1%)	1,296 (60.2%)	62,294 (44.9%)	**<0.001**
Ischemic heart disease, n (%)	69 (10.1%)	325 (15.1%)	13,895 (10.0%)	**<0.001**
Malignancy, n (%)	88 (12.9%)	384 (17.8%)	13,296 (9.6%)	**<0.001**
Chronic renal failure, n (%)	20 (2.9%)	73 (3.4%)	5,127 (3.7%)	0.444

Abbreviations: n, Number; SD, standard deviation; BMI, body mass index

[a] This group encompasses untreated patients or patients treated by topical treatments, phototherapy, Dead Sea climate therapy, or acitretin

Table 2- The risk of COVID-19 and its complications among patients with psoriasis treated by IL-17 inhibitors compared to those treated by methotrexate (main analysis)

	COVID-19 infection		**COVID-19-associated hospitalization**		**COVID-19-associated mortality**	
	IL-17 inhibitors (N=680)	**Methotrexate (N=2,153)**	**IL-17 inhibitors (N=680)**	**Methotrexate (N=2,153)**	**IL-17 inhibitors (N=680)**	**Methotrexate (N=2,153)**
Follow-up time, PY	411.0	1,299.1	412.8	1,302.6	413.0	1,304.8
Median follow-up time, years (range)	**0.6 (0.0-0.6)**	**0.6 (0.1-0.6)**	**0.6 (0.0-06)**	**0.6 (0.1-0.6)**	**0.6 (0.0-06)**	**0.6 (0.1-0.6)**
Number of events	13	42	1	11	1	1
Incidence rate / 1000 PY (95% CI)	31.6 (17.6-52.7)	32.3 (23.6-43.3)	2.4 (0.1-12.0)	8.4 (4.4-14.7)	2.4 (0.1-11.9)	0.8 (0.1-3.8)
Unadjusted HR (95% CI) [P value]	0. 98(0.52-1.82) [0.940]	Reference	0.29 (0.04-2.22) [0.231]	Reference	3.15 (0.20-50.35) [0.417]	Reference
Male-specific HR (95% CI) [P value]	0.94 (0.37-2.37) [0.869]	Reference	0.03 (0.00-24.90) [0.309]	Reference	NA [0.719]	Reference
Female-specific HR (95% CI) [P value]	1.03 (0.45-2.40) [0.941]	Reference	1.18 (0.12-11.33) [0.887]	Reference	NA [0.647]	Reference
Age- and sex-Adjusted HR (95% CI) [P value]	0.93 (0.49-1.74) [0.821]	Reference	0.39 (0.05-3.09) [0.372]	Reference	7.67 (0.41-142.89) [0.172][b]	Reference

Fully adjusted HR (95% CI) [P value][a]	0.91 (0.48-1.72) [0.779][a]	Reference	0.42 (0.05-3.39) [0.413][a]	Reference	7.57 (0.36-157.36) [0.191][a]	Reference

[a]-Multivariate logistic regression model adjusting for age, sex, ethnicity, comorbidities (as estimated by CCI), and smoking

Abbreviations: n, Number; PY, person-year; HR, hazard ratio; CI, confidence interval.

Bold: significant value

Table 3- The risk of COVID-19 and its complications among patients with psoriasis treated by IL-17 inhibitors as compared to those without systemic immunosuppressive/ immunomodulatory drugs (secondary analysis)

	COVID-19 infection		**COVID-19-associated hospitalization**		**COVID-19-associated mortality**	
	IL-17 inhibitors (N=680)	**Non-systemic treatment (N=138,750)***	**IL-17 inhibitors (N=680)**	**Non-systemic treatment (N=138,750)***	**IL-17 inhibitors (N=680)**	**Non-systemic treatment (N=138,750)***
Follow-up time, PY	411.0	83,666.6	412.8	84,068.7	413.0	84,119.4
Median follow-up time, years (range)	0.6 (0.0-0.6)	0.6 (0.0-0.6)	0.6 (0.0-06)	3.7 (3.3-4.2)	0.6 (0.0-06)	0.6 (0.0-0.6)
Number of events	13	3,033	1	314	1	48
Incidence rate / 1000 PY (95% CI)	31.6 (17.6-52.7)	36.3 (35.0-37.6)	2.4 (0.1-12.0)	8.4 (4.4-14.7)	2.4 (0.1-11.9)	0.6 (0.4-0.8)
Unadjusted HR (95% CI) [P value]	0.87 (0.50-1.50) [0.619]	Reference	0.65 (0.09-4.62) [0.648]	Reference	4.24 (0.59-30.71) [0.153]	Reference
Male-specific HR (95% CI) [P value]	0.77 (0.35-1.72) [0.522]	Reference	0.05 (0.01-503.72) [0.523]	Reference	NA [0.795]	Reference
Female-specific HR (95% CI) [P value]	0.99 (0.47-2.07) [0.971]	Reference	1.55 (0.21-11.08) [0.662]	Reference	**11.22 (1.51-83.62) [0.018]**	Reference
Age- and sex-Adjusted HR (95% CI) [P value]	0.92 (0.52-1.55) [0.709]	Reference	0.67 (0.09-4.79) [0.673]	Reference	7.25 (0.99-53.12) [0.051][b]	Reference
Fully adjusted HR	0.92 (0.54-	Reference	0.65 (0.09-4.59)	Reference	7.05 (0.96-	Reference

(95% CI) [P value][a]	1.59) [0.776][a]	[0.662][a]	51.98) [0.055][a]

* This group encompasses untreated patients or patients treated by topical treatments, phototherapy, Dead Sea climate therapy, or acitretin

[a]-Multivariate logistic regression model adjusting for age, sex, ethnicity, comorbidities (as estimated by CCI), and smoking

Abbreviations: n, Number; PY, person-year; HR, hazard ratio; CI, confidence interval.

Bold: significant value

Supplementary table 1- The risk of COVID-19 and its complications among patients with psoriasis treated by secukinumab as compared to those treated by methotrexate (sensitivity analysis)

	COVID-19 infection		**COVID-19-associated hospitalization**		**COVID-19-associated mortality**	
	Secukinumab (N=451)	**Methotrexate (N=2,153)**	**Secukinumab (N=451)**	**Methotrexate (N=2,153)**	**Secukinumab (N=451)**	**Methotrexate (N=2,153)**
Follow-up time, PY	272.3	1,299.1	273.7	1,302.6	273.7	1,304.8
Median follow-up time, years (range)	0.6 (0.0-0.6)	0.6 (0.1-0.6)	0.6 (0.0-0.6)	0.6 (0.1-0.6)	0.6 (0.0-0.6)	0.6 (0.1-0.6)
Number of events	9	42	0	11	0	1
Incidence rate / 1000 PY (95% CI)	33.1 (16.1-60.7)	32.3 (23.6-43.3)	0	8.4 (4.4-14.7)	0	0.8 (0.1-3.8)

Unadjusted HR (95% CI) [P value]	1.02 (0.50-2.09) [0.956]	Reference	0.04 (0.00-31.42) [0.338]	Reference	NA [0.773]	Reference
Male-specific HR (95% CI) [P value]	1.21 (0.45-3.27) [0.702]	Reference	0.04 (0.00-77.38) [0.396]	Reference	NA [0.764]	Reference
Female-specific HR (95% CI) [P value]	0.87 (0.30-2.59) [0.789]	Reference	0.04 (0.00-23,075.03) [0.630]	Reference	NA	Reference
Age- and sex-Adjusted HR (95% CI) [P value]	0.92 (0.44-1.90) [0.818]	Reference	NA [0.980]	Reference	NA [0.987]	Reference
Fully-adjusted HR (95% CI) [P value][a]	0.93 (0.45-1.94) [0.852]	Reference	NA[a] [0.937]	Reference	NA[a] [0.982]	Reference

[a]-Multivariate logistic regression model adjusting for age, sex, ethnicity, comorbidities (as estimated by CCI), and smoking

Abbreviations: n, Number; PY, person-year; HR, hazard ratio; CI, confidence interval.

Bold: significant value

Supplementary table 2- The risk of COVID-19 and its complications among patients with psoriasis treated by ixekizumab as compared to those treated by methotrexate (sensitivity analysis)

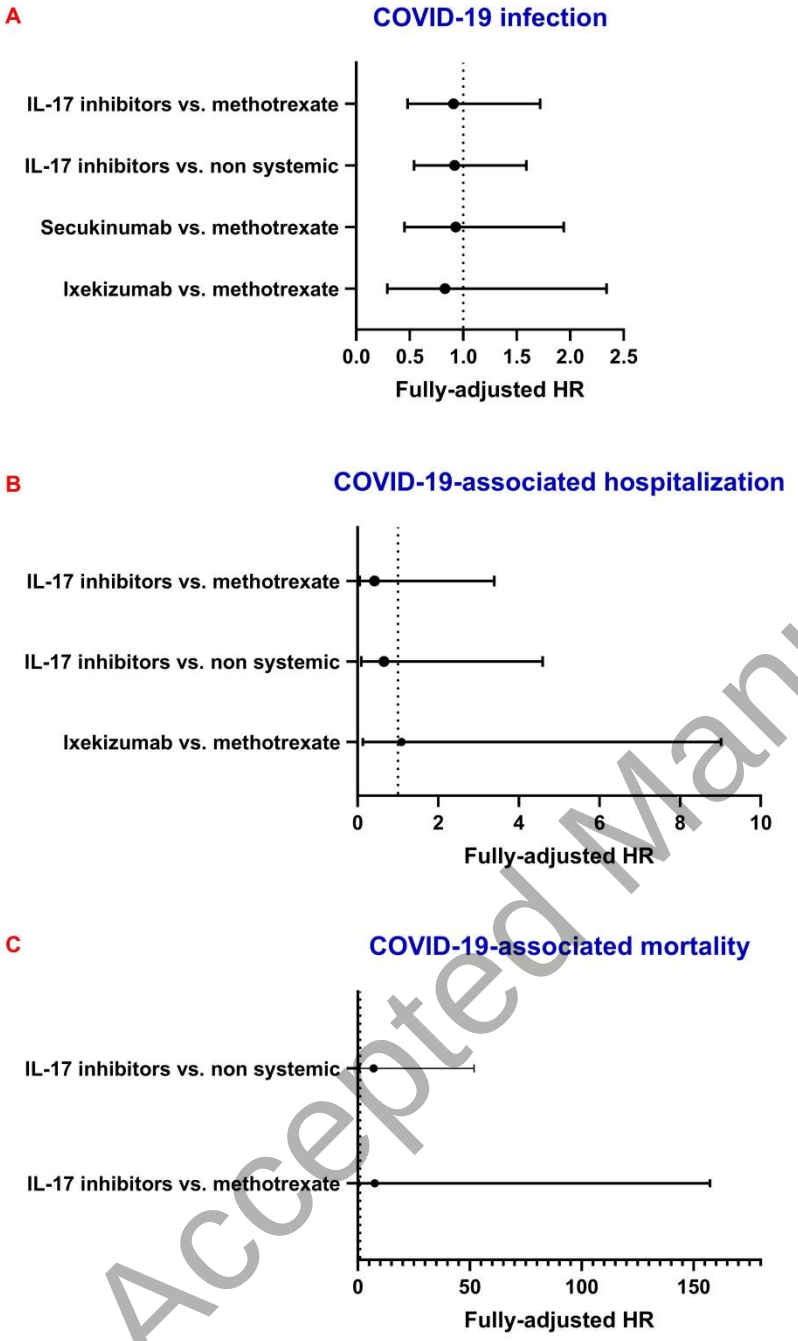
	COVID-19 infection		**COVID-19-associated hospitalization**		**COVID-19-associated mortality**	
	Ixekizumab (N=249)	**Methotrexate (N=2,153)**	**Ixekizumab (N=249)**	**Methotrexate (N=2,153)**	**Ixekizumab (N=249)**	**Methotrexate (N=2,153)**
Follow-up time, PY	150.9	1,299.1	151.2	1,302.6	151.4	1,304.8
Median follow-up time, years (range)	0.6 (0.4-0.6)	0.6 (0.1-0.6)	0.6 (0.4-0.6)	0.6 (0.1-0.6)	0.6 (0.4-0.6)	0.6 (0.1-0.6)
Number of events	4	42	1	11	1	1
Incidence rate / 1000 PY (95% CI)	26.5 (8.4-63.9)	32.3 (23.6-43.3)	6.6 (0.3-32.6)	8.5 (4.4-14.7)	6.6 (0.3-32.6)	0.8 (0.0-3.8)
Unadjusted HR (95% CI) [P value]	0. 82(0.29-2.28) [0.700]	Reference	0.79 (0.10-6.06) [0.815]	Reference	8.59 (0.54-137.31) [0.128]	Reference
Male-specific HR (95% CI) [P value]	0.42 (0.06-3.12) [0.394]	Reference	0.04 (0.00-509.36) [0.507]	Reference	NA [0.815]	Reference
Female-specific HR (95% CI) [P value]	1.24 (0.37-4.11) [0.727]	Reference	3.31 (0.34-31.82) [0.300]	Reference	NA [0.948]	Reference
Age- and sex-Adjusted HR (95% CI) [P value]	0. 80(0.29-2.23) [0.666]	Reference	1.04 (0.13-8.22) [0.973]	Reference	19.79 (0.98-363.46) [0.051][b]	Reference
Fully adjusted HR	0.83 (0.29-2.34)	Reference	1.09 (0.13-	Reference	27.09 (0.95-	Reference

(95% CI) [P value][a]	[0.718][a]	9.02) [0.935][a]	772.05) [0.054][a]

[a]-Multivariate logistic regression model adjusting for age, sex, ethnicity, comorbidities (as estimated by CCI), and smoking

Abbreviations: n, Number; PY, person-year; HR, hazard ratio; CI, confidence interval.

Bold: significant value



Legends to figures

Figure 1: Fully adjusted hazard ratios (HRs) of COVID-19 (A), COVID-19-associated hospitalization (B), and COVID-19-associated mortality (c) in patients with psoriasis treated by interleukin 17 inhibitors relative to those treated by methotrexate and non-systemic/non-immunomodulatory treatments