Hepatitis Virus Reactivation in Patients with Psoriasis Treated with Secukinumab in a Real-World Setting of Hepatitis B or Hepatitis C Infection

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Abstract
Background and Objective Biologics for psoriasis, especially anti-tumor necrosis factor-α therapies, may reactivate hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, as well in inactive carriers or patients with occult infection. However, some biologics, including anti-interleukin-17 therapies such as secukinumab, seem to be less likely to cause hepatitis reactivation. This study assessed the safety of secukinumab treatment in patients with psoriasis with HBV or HBC infection.

Methods This was a retrospective cohort study of patients with moderate-to-severe psoriasis treated with secukinumab at seven Italian centers. Patients serologically positive for one or more of the following viral hepatitis markers were included: HCV antibody (± HCV-RNA positivity) and/or hepatitis B surface antigen, and/or HBV core antibody and/or HBV surface antibody (± HBV-DNA positivity). Patients received secukinumab 300 mg subcutaneously at week 0/1/2/3/4 then every 4 weeks; prophylactic therapy before starting secukinumab was prescribed where indicated. The primary study endpoint was the reactivation of hepatitis viral infection, defined as conversion to HBV-DNA or HCV-RNA positivity, with or without elevation of transaminases.

Results Sixty patients (17 with concomitant psoriatic arthritis) were included. Thirteen subjects were hepatitis B surface antigen positive, 19 were HBV core antibody positive, and 30 were positive for the HCV antibody; however, all were HCV-RNA negative. After 53.5 ± 37.5 weeks of secukinumab therapy, hepatitis reactivation occurred in only one patient, who had a reactivation of both hepatitis B and hepatitis C. This patient had not undergone hepatitis B prophylaxis or hepatitis C treatment before secukinumab.

Conclusions These real-world data support the safety of secukinumab in patients with positive markers of HBV or HCV infection, when administered together with dedicated prophylaxis.

Plain Language Summary
In this retrospective cohort study, 60 patients with moderate-to-severe psoriasis were treated with secukinumab at seven Italian centers. Secukinumab is a fully human monoclonal antibody targeting interleukin-17A, a key cytokine associated with the development of psoriatic disease. All patients had markers of hepatitis B and/or C. Where appropriate, patients received...
prophylactic antiviral therapy before starting secukinumab at the standard dose for treating psoriasis in Italy. Secukinumab was administered at the labeled dose. After a mean duration treatment of 53.5 weeks, hepatitis reactivation (both B and C) occurred in one patient. This patient had not undergone hepatitis B prophylaxis or hepatitis C treatment before receiving secukinumab. The study is important, as some biologics for psoriasis, especially anti-tumor necrosis factor-α therapies, have been shown to reactivate both hepatitis B virus or hepatitis C virus infections in inactive carriers, patients with occult hepatitis B virus infection, or patients with hepatitis C virus infections. However, there is evidence that second-generation biologic therapies, including those with anti-interleukin-17 activity, are less likely to cause hepatitis reactivation. This study supports the safety of secukinumab treatment in patients with psoriasis with hepatitis B and/or C.

**Key Points**

In this retrospective cohort study, 60 patients with moderate-to-severe psoriasis were treated with secukinumab.

After a mean duration treatment of 53.5 weeks, hepatitis reactivation (both B and C) occurred in 1 patient, who had not undergone hepatitis B prophylaxis or hepatitis C treatment before receiving secukinumab.

This study supports the safety of secukinumab treatment in psoriasis patients with hepatitis B and/or C.

1 Introduction

Biologic therapies are the cornerstone therapy for immune-mediated inflammatory diseases, including plaque psoriasis and psoriatic arthritis [1–5]. The decision-making process for biologic therapy should also include screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection [3, 6–9]. Indeed, some biologics may reactivate HBV or HCV infections, with consequent morbidity and mortality [10–16]. Therefore, the presence or absence of hepatitis is among factors to be considered when selecting the most appropriate psoriasis therapy [17, 18]. Patients showing positivity for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBcAg), especially, should undergo prophylactic antiviral treatment with lamivudine or entecavir prior to the initiation of biologic therapy [1, 3, 6, 9, 10]. The risk of viral reactivation or opportunistic infections is reported to be higher with anti-tumor necrosis factor-α therapies [10, 16, 19–21]. However, there is increasing evidence that some biologics, including those with anti-interleukin (IL)-17 activity, are less likely to cause hepatitis B or C reactivation than anti-tumor necrosis factor-α agents [15, 22].

Interleukin-17A is a key cytokine in the development of psoriatic disease [23, 24]. Furthermore, increased serum levels of IL-17 and circulating T-helper 17 cells have been shown to be the indicators of activation and progression of HBV infection [25, 26]. Secukinumab, a fully human monoclonal antibody targeting IL-17A, selectively binds and neutralizes IL-17A as both homodimer and heterodimeric ligands of IL-17 [27], and has shown high efficacy together with a favorable safety profile in clinical trials [28–33].

There have been numerous case reports and case series reporting the safety of secukinumab in patients with hepatitis B or C [34–42]. However, a multicentric prospective cohort study involving 63 patients with concurrent HBV/HCV infection showed that, in the absence of antiviral prophylaxis, 7 of 46 (15.2%) of the patients with HBV exhibited viral reactivation during secukinumab therapy [19]. The risk of reactivation was significantly higher in HBsAg-positive patients, compared with HBsAg-negative/HBcAb-positive patients (24.0 vs 4.17%, \( p = 0.047 \)). However, no virus reactivation occurred in patients receiving antiviral prophylaxis. As a consequence, patients with psoriasis and HBV infection (especially if HBsAg positive and HBsAg negative/HBcAb positive) undergoing secukinumab treatment need prophylactic antiviral treatment and/or close monitoring of the viral load. In particular, antiviral prophylaxis should be mandatory for all HBsAg-positive patients. To gain more data on the safety of secukinumab in this scenario, we collected data on patients with hepatitis B or C who underwent secukinumab treatment for psoriasis to assess its safety profile in this class of patients.

2 Patients and Methods

2.1 Study Participants

A multicenter retrospective cohort study of patients with moderate-to-severe psoriasis treated with secukinumab between 2018 and 2021 was conducted at seven Italian centers (Department of Dermatology, University of Naples Federico II, Naples; Dermatology Unit, University of Campania Luigi Vanvitelli, Naples; Department of Medicine, Surgery and Dentistry, “Scuola Medica Salernitana” University of Salerno, Salerno; Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro; Department of Biomedical Sciences and Human Oncology, Section of Dermatology, University of Bari, Bari; Department of Clinical and
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Experimental Medicine, Section of Dermatology, University of Messina, Messina; Section of Dermatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties “G. D’Alessandro” [PROMISE], University of Palermo, Palermo).

All patients were screened for HBV and HCV before secukinumab was started. Patients who were serologically positive for one or more of the following viral hepatitis markers were included in the study: anti-HCV (with or without HCV-RNA positivity) and/or HBsAg, and/or HBV core antibody (HBcAb) and/or HBV surface antibody (HBsAb) [with or without HBV-DNA positivity].

Patients with viral hepatitis markers for HCV or HBV were referred to an infectivologist or hepatologist for further evaluation and eventual prescription of prophylactic therapy before secukinumab administration was started. Secukinumab therapy was administered at the labeled dose for psoriasis in Italy: 300 mg subcutaneously at week 0, 1, 2, 3, and 4, then 300 mg every 4 weeks.

Institutional ethics approval for the study was obtained from the local ethics committee or institutional review board at each participating institution, and the study was conducted in accordance with the principles of the 1975 Declaration of Helsinki and its amendments, the International Conference of Harmonization Good Clinical Practice, and all applicable laws and regulations. Patients were not required to give additional informed consent for participation in the study as all patients had agreed to be followed up and for clinical records to be collected by the institutions at the time of being prescribed secukinumab and only anonymized data were used in the analysis.

2.2 Data Collection

At each center, data were anonymously collected from patient charts and assembled in an electronic database for analysis. Demographic, clinical, and standard laboratory data were extracted, including age, sex, psoriasis duration, comorbidities including psoriatic arthritis, previous treatment for psoriasis, prophylactic regimen and duration of prophylaxis, levels of transaminases, and HBV and HCV serostatus and how quantified.

2.3 Outcome

The primary study outcome was the reactivation of hepatitis viral infection, defined as conversion to HBV-DNA or HCV-RNA positivity with or without elevation of transaminases or HBV-DNA or HCV-RNA viral load increase. Response to secukinumab or treatment-emergent adverse events were not the aim of the study and were not recorded. Data were analyzed with descriptive statistics.

3 Results

Sixty patients with moderate-to-severe plaque psoriasis were enrolled (35 male and 25 female) with a mean age of 59.3 ± 9.1 years. Patient demographic and clinical characteristics at baseline are summarized in Table 1. The mean duration of psoriasis was 13.3 ± 11.6 years, and 17 patients (28.3%) were also affected by psoriatic arthritis with a mean disease

| Table 1 | Baseline demographic and clinical characteristics (n = 60) |
|-----------------|-----------------|
| Characteristic | Values |
| Age, mean ± SD, years | 59.3 ± 9.1 |
| Sex, n (%) | |
| Female | 25 (41.7) |
| Male | 35 (58.3) |
| Psoriasis duration, mean ± SD, years | 13.3 ± 11.6 |
| Psoriatic arthritis, n (%) | 17 (28.3) |
| Duration, mean ± SD, years | 7.8 ± 7.1 |
| Comorbidities, n (%) | |
| Hypertension | 41 (68.3) |
| Dyslipidemia | 27 (45.0) |
| Diabetes mellitus | 21 (35.0) |
| Cardiopathy | 17 (28.3) |
| Othersa | 12 (20.0) |
| Prior systemic treatment for psoriasis, n (%) | |
| Cyclosporine | 31 (51.7) |
| Methotrexate | 21 (35.0) |
| Phototherapy | 17 (28.3) |
| Adalimumab | 14 (23.3) |
| Ustekinumab | 11 (18.3) |
| Acitretin | 9 (15.0) |
| Etanercept | 6 (10.0) |
| Infliximab | 3 (5.0) |
| Golimumab | 2 (3.3) |
| Transaminase values, IU/mL, mean ± SD | |
| Aspartate aminotransferase | 31.4 ± 15.8 |
| Alanine aminotransferase | 27.9 ± 18.6 |
| HBV/HCV-associated features, n (%) | |
| HBsAg positive | 13 (21.7) |
| HBeAb positive | 19 (31.7) |
| HBsAb positive | 16 (26.7) |
| HBeAg positive | 1 (16.7) |
| HBeAb positive | 4 (6.7) |
| Anti-HCV antibody positive | 30 (50.0) |
| HCV-RNA positive | 0 (0.0) |

aAutoimmune disease (n = 5), anxiety (n = 3), and chronic obstructive pulmonary disease, renal failure, fibromyalgia, and HIV infection in one patient each

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duration of 7.8 ± 7.1 years. Comorbidities were prevalent in our sample (Table 1). Forty-one patients had hypertension, 27 had dyslipidemia, 21 had diabetes mellitus, and 17 had cardiopathy.

The most common previous systemic treatments for psoriasis are shown in Table 1. Thirty-one patients had received cyclosporine, 21 methotrexate, 17 phototherapy, 14 adalimumab, 11 ustekinumab, 9 acitretin, 6 etanercept, 3 infliximab, and 2 golimumab.

Baseline transaminase values prior to the initiation of secukinumab were aspartate aminotransferase (AST) of 31.4 ± 15.8 IU/mL and alanine aminotransferase (ALT) of 27.9 ± 18.6 IU/mL. At baseline, of the 60 patients, 13 (21.7%) had HBsAg positivity, 19 (31.7%) had HBcAb positivity, 16 (26.7%) had HBeAg positivity, 1 (1.7%) had hepatitis B e-antigen (HBeAg) positivity, and 4 (6.7%) had hepatitis B e-antibody (HBeAb) positivity. In addition, 30 (50%) subjects were seropositive for the anti-HCV antibody, but all were HCV-RNA negative.

### 3.1 HBV Infection

All 13 patients with HBsAg positivity at baseline underwent antiviral prophylaxis prior to secukinumab initiation [12 (92.3%) with lamivudine and 1 (7.7%) with entecavir]. Two out of 13 (15.4%) also had HBsAb positivity, 1 (7.7%) had HBeAg positivity, 2 (14.4%) had HBeAb positivity, and 1 (7.7%) had HBcAb positivity. Among 19 patients with HBcAb positivity, 14 (73.7%) also had HBsAb positivity, and 4 (21%) had HBeAb positivity. HBV-DNA was negative in 18/19 (94.7%) subjects. Of the 19 patients who showed HBcAb positivity, only two (10.5%) had undergone antiviral prophylaxis before secukinumab initiation (one with entecavir and one with lamivudine). Of note, one of these two patients showed HBV-DNA positivity. Following the directives of the hepatologist and/or infectivologist, the remaining 17 patients with HBcAb positivity, all showing HBV-DNA negativity, started secukinumab without prophylaxis together with trimestral monitoring of HBV markers, HBV-DNA, AST, and ALT.

After secukinumab therapy for a mean duration of 53.5 ± 37.5 weeks (range 16–240 weeks), hepatitis B reactivation was observed in only one patient. Specifically, this was a patient with the following hepatitis B markers at baseline: HBsAg and HBV-DNA negativity, HBcAb and HBsAb positivity, and markers of HCV infection (anti-HCV positive and HCV-RNA negative). This patient did not undergo hepatitis B prophylaxis and experienced hepatitis B reactivation after 48 weeks of secukinumab therapy, at which time AST was 112 IU/mL and ALT was 119 IU/mL. Hepatitis B surface antigen turned positive and HBV-DNA turned positive with a value of 400,000 IU/mL. Secukinumab was discontinued, and the patient started entecavir therapy. The same patient also had hepatitis C reactivation after 48 weeks of secukinumab, with HCV-RNA of 2,000,000 copies/mL. Of note, he had not undergone hepatitis C treatment before secukinumab because he was HCV-RNA negative at that time.

### 3.2 HCV Infection

Thirty (50%) subjects were seropositive for the anti-HCV antibody, but all were HCV-RNA negative. Of these patients, two also had HBsAg positivity, five had HBcAb positivity, five had HBsAb positivity, one had HBeAb positivity, and one was HBV-DNA positive. The latter patients started lamivudine prophylaxis before treatment with secukinumab was initiated. No subject underwent hepatitis C treatment before secukinumab initiation. As noted, there was one case of HCV reactivation in a patient with markers of hepatitis B infection.

### 4 Discussion

Biologic agents used to treat chronic immune-mediated inflammatory diseases can be immunogenic, leading to anti-drug antibodies that adversely affect response and can cause hypersensitivity reactions. Hepatitis B virus and HCV reactivation has been reported in patients infected with HBV or HCV, and current guidelines recommend screening for hepatitis status before initiating biologic therapy and anti-HBV prophylaxis in HBV carriers before starting immunosuppressive therapy [3, 6, 9, 10].

Joint guidelines of care for the management and treatment of patients with psoriasis with biologics have been issued by the American Academy of Dermatology and the National Psoriasis Foundation [1]. As for other biologics, including IL-12/23 inhibitors and tumor necrosis factor-α inhibitors, caution is recommended for the use of IL-17 inhibitors in patients with pre-existing immunosuppression-related conditions. However, both societies support the use of an IL-17 inhibitor for psoriasis in patients with a history of or currently active HCV infection and recommend concomitant management by an appropriate healthcare provider [1]. For patients with currently active hepatitis B, an IL-17 inhibitor is recommended after an initial evaluation and determination of concomitant antiviral medication for hepatitis B guided by testing for HBcAb positivity. Patients with a history of hepatitis B confirmed as resolved do not need a specialist follow-up, but monitoring is required because of the risk of reactivation [1]. Thus, although secukinumab has a lower potential for immunogenicity than other biologics [43–46], screening for hepatitis B in patients with psoriasis should still be considered essential before biologic initiation as well as a referral to an infectivologist and eventual prophylactic treatment to be evaluated case by case. The presence of risk
factors should also be taken into consideration. In particular, prophylactic treatment is mandatory when HBsAg is positive, while HBCaB positivity in the context of HBsAg negativity needs personalized management following individual risk factors [47]. Of particular note, when HBV prophylaxis is to be initiated, it should be started at least 1–2 weeks before administration of a biologic and continued for up to 6 months after biologic discontinuation [47].

Our study supports the safety of secukinumab therapy when associated with hepatitis B prophylaxis in patients with psoriasis with HBsAg positivity. Indeed, we observed no cases of hepatitis B reactivation in those patients. Secukinumab also appears to be safe in HBCaB-positive patients with or without HBsAb positivity. However, HBsAg and HBV-DNA, and AST and ALT monitoring is needed. Notably, we observed only one case of HBV reactivation, in a patient with HBCaB and HBsAb positivity with HBV-DNA negativity and who had not undergone HBV prophylaxis treatment. Hence, screening for markers of HBV and HCV is mandatory prior to secukinumab treatment.

Moreover, close monitoring of hepatitis markers is advisable during secukinumab treatment in the case of HBCaB positivity with HBsAg and HBV-DNA negativity. Nevertheless, HBV reactivation with secukinumab is uncommon. Positivity for HBsAg always requires prophylaxis before secukinumab is initiated. In the case of HBsAg negativity and HBCaB positivity, prophylaxis or monitoring of viral markers and transaminases can be chosen following negativity or positivity of HBV-DNA, taking into consideration the risk factors of the patient and after referral to the hepatologist and/or infectiologist.

Finally, secukinumab also seemed safe to use in patients with antibodies against hepatitis C. We observed only one case of HCV reactivation out of 30 patients with anti-HCV positivity and HCV-RNA negativity. Interestingly, this patient also showed concomitant HBV infection and concomitant HBV reactivation (hepatitis markers at baseline: HBsAg and HBV-DNA negativity, HBCaB and HBsAb positivity, anti-HCV positivity, and HCV-RNA negativity) after 48 weeks of secukinumab treatment. Hence, additional individual risk factors or other peculiarities that may have influenced the reactivation, apart from the treatment, cannot be excluded because reactivation was experienced after 48 weeks of therapy. However, it should be noted that the risk of reactivation is higher with HBV than HCV [15, 47], and the issue could be further minimized now that definitive treatments for HCV infection are available.

A strength of our study is the inclusion of a population that is often excluded from or under-represented in clinical trials, delivering data from a cross-section of patients with a range of comorbidities more representative of those seen in real-world clinical practice. However, we acknowledge the potential limitations of our study because of its retrospective design and lack of a comparison group of patients with HBV or HCV not treated with secukinumab or treated with other biologics. There were also a limited number of patients in each serological, virologic, and biochemical category of hepatitis infection. Furthermore, patients had undergone a range of prior systemic treatments for psoriasis before secukinumab treatment was initiated.

5 Conclusions

Secukinumab seems to be safe in patients with positive markers of HBV or HCV infection when administered together with dedicated prophylaxis. Conversely, in the absence of antiviral prophylaxis, the incidence of HCV reactivation is very low but still possible. However, regarding HBCaB positivity with HBsAg and HBV DNA negativity, prophylaxis should be evaluated on a case-by-case basis. Indeed, we observed only one case of HBV reactivation during secukinumab therapy in this category of patients, which requires a personalized approach following individual risk factors.

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Declarations

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Conflict of interest Matteo Megna has acted as a speaker or consultant for Abbvie, Amgen, Eli Lilly, Leo Pharma, Janssen, Novartis, and UCB. Gabriella Fabbrocini has acted as a speaker or consultant for Abbvie, Almirall, Amgen, Eli Lilly, Leo Pharma, Janssen, Novartis, Sanofi, and UCB. Cataldo Patruno has acted as an advisor, consultant, speaker, and/or investigator for Abbvie, Amgen, Eli Lilly, Leo Pharma, Novartis, Pfizer, Pierre Fabre, and Sanofi. Claudio Guarnieri has received consultation fees and/or grants for research projects and advisory panels and for giving educational lectures from Wyeth-Pfizer, Abbott Immunology-Abbvie, Janssen-Cilag, Novartis, LEO-Pharma, Ely-Lilly, Celgene, Merck-Serono, Sanofi-Aventis, Amgen, and Almirall. The other authors declare no conflicts of interest.

Ethics approval All procedures related to this work adhered to the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, and its amendments. This study received approval from the local ethics committee or institutional review board at each participating institution.

Consent to participate Informed consent was obtained from the patients at the time of being prescribed secukinumab. Additional consent for participation in the study was not required and only anonymized data were used in the analysis.

Consent for publication Not applicable.
Availability of data and material  The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability  Not applicable.

Author contributions  All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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