

## Management of psoriasis patients with hepatitis B or hepatitis C virus infection

Claudio Bonifati, Viviana Lora, Dario Graceffa, Lorenzo Nosotti

Claudio Bonifati, Viviana Lora, Dario Graceffa, Center for the Study and Treatment of Psoriasis San Gallicano Dermatologic Institute, IRCCS, 00144 Rome, Italy

Lorenzo Nosotti, Gastrointestinal and Liver Department, National Institute for Health, Migration and Poverty, 00153 Rome, Italy

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**Correspondence to:** Claudio Bonifati, MD, Center for the Study and Treatment of Psoriasis San Gallicano Dermatologic Institute, IRCCS, ViaElioChianesi 53, 00144 Rome, Italy. [psoriasi@ifo.gov.it](mailto:psoriasi@ifo.gov.it)  
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### Abstract

The systemic therapies available for the management

of Psoriasis (PsO) patients who cannot be treated with more conservative options, such as topical agents and/or phototherapy, with the exception of acitretin, can worsen or reactivate a chronic infection. Therefore, before administering immunosuppressive therapies with either conventional disease-modifying drugs (cDMARDs) or biological ones (bDMARDs) it is mandatory to screen patients for some infections, including hepatitis B virus (HBV) and hepatitis C virus (HCV). In particular, the patients eligible to receive an immunosuppressive drug must be screened for the following markers: antibody to hepatitis B core, antibody to hepatitis B surface antigen (anti-HBsAg), HBsAg, and antibody to HCV (anti-HCV). In case HBV or HCV infection is diagnosed, a close collaboration with a consultant hepatologist is needed before and during an immunosuppressive therapy. Concerning therapy with immunosuppressive drugs in PsO patients with HBV or HCV infection, data exist mainly for cyclosporine a (CyA) or bDMARDs (etanercept, adalimumab, infliximab, ustekinumab). The natural history of HBV and HCV infection differs significantly as well as the effect of immunosuppression on the aforementioned infectious diseases. As a rule, in the case of active HBV infection, systemic immunosuppressive antipsoriatic therapies must be deferred until the infection is controlled with an adequate antiviral treatment. Inactive carriers need to receive antiviral prophylaxis 2-4 wk before starting immunosuppressive therapy, to be continued after 6-12 mo from its suspension. Due to the risk of HBV reactivation, these patients should be monitored monthly for the first 3 mo and then every 3 mo for HBV DNA load together with transaminases levels. Concerning the patients who are occult HBV carriers, the risk of HBV reactivation is very low. Therefore, these patients generally do not need antiviral prophylaxis and the sera HBsAg and transaminases dosing can be monitored every 3 mo. Concerning PsO patients with chronic HCV infection their management with immunosuppressive drugs is less problematic as compared to those infected by HBV.

In fact, HCV reactivation is an extremely rare event after administration of drugs such as CyA or tumor necrosis factor- $\alpha$  inhibitors. As a rule, these patients can be monitored measuring HCV RNA load, and ALT, aspartate transaminase, gamma-glutamyl-transferase, bilirubin, alkaline phosphatase, albumin and platelet every 3-6 mo. The present article provides an updated overview based on more recently reported data on monitoring and managing PsO patients who need systemic antipsoriatic treatment and have HBV or HCV infection as comorbidity.

**Key words:** Psoriasis; Therapy; Conventional disease-modifying drugs; Biological disease-modifying drugs; Hepatitis B virus infection; Hepatitis C virus infection

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**Core tip:** At present, no guidelines give clear indications regarding the management of psoriasis patients with concomitant hepatitis B or hepatitis C virus infection who need a systemic treatment. On the basis of the available literature data, this paper provides an overview in this field from a practical point of view. A particular emphasis is given, with regard to the use of biological drugs, in the aforementioned patients.

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## INTRODUCTION

Psoriasis (PsO) is a frequent inflammatory immunomediated disease affecting approximately 2% of the population<sup>[1]</sup>. Various clinical types of psoriasis exist. The plaque-type, also known as psoriasis vulgaris (PV), is the most common form (80%-90% of the cases)<sup>[2]</sup>. Typical lesions of PV are represented by monomorphic, sharply demarcated erythematous plaques covered by silvery lamellar scales. From 70% to 80% of patients are affected by limited forms of PsO and need to be treated only with topical and or photo-therapy<sup>[2]</sup>. Patients with more extensive PsO (> 10% of the body surface area) or psoriatic arthritis (PsA) are in greater need of treatment. For these patients prolonged systemic therapies are often necessary<sup>[2-4]</sup>.

The therapeutic armamentarium available for the cure of PsO encompasses the conventional disease-modifying drugs (cDMARDs) and biological DMARDs (bDMARDs) (Table 1).

cDMARDs represent the first line of therapies in high-need psoriatic patients, while bDMARDs are for those subjects in whom cDMARDs have either failed,

**Table 1 Therapies approved by European Medicines Agency for the treatment of psoriasis**

	Recommended doses for adult patients
Conventional DMARDs	
Acitretine	0.25-1 mg/kg per day
Cyclosporin a	2-5 mg/kg per day
Methotrxate	10 mg to 25 mg per week
Biologic DMARDs	
Infliximab	5 mg/kg at 0, 2 and 6 wk followed by a maintenance regimen of 5 mg/kg every 8 wk
Adalimumab	80 mg initially, 40 mg on day 8, and 40 mg every other week thereafter
Etanercept	50 mg subcutaneously 2 times a week for 3 mo; (starting doses of 50 mg once a week have been shown to be effective); maintenance: 50 mg subcutaneously once a week
Golimumab <sup>1,2</sup>	50 mg once a month
Certolizumab pegol <sup>1,2</sup>	400 mg at 0, 2 and 4 wk followed by a maintenance regimen of 200 mg every other week
Ustekinumab <sup>3</sup>	45 mg initially, 45 mg at 4 wk, followed by a maintenance regimen of 45 mg every 12 wk <sup>3</sup>
Secukinumab <sup>2</sup>	300 mg at 0, 1, 2, 3, and 4 wk followed by a maintenance regimen of 300 mg every 4 wk. For some patients, a dose of 150 mg may be acceptable

<sup>1</sup>Approved for adults with active psoriatic arthritis; <sup>2</sup>No data available regarding the administration of patients with HBV or HCV; <sup>3</sup>For patients weighing > 100 kg (220 lbs), the recommended dose is 90 mg initially, 90 mg at 4 wk, followed by a maintenance regimen of 90 mg every 12 wk. HBV: Hepatitis B virus; HCV: Hepatitis C virus.

were not tolerated, or were contraindicated<sup>[5-8]</sup>.

The choice of a systemic treatment depends upon several variables linked to both the characteristics of a given patient and those of the drug administered.

Regarding the systemic treatments currently available for PsO, with the exception of acitretin, all the other drugs listed in Table 1 are immunosuppressive<sup>[9-11]</sup>. Therefore, the guidelines presently available, although with some differences among them, recommend screening PsO patients for some common infectious diseases [human immunodeficiency virus, latent tuberculosis, hepatitis B virus (HBV) and hepatitis C virus (HCV)] before starting an immunosuppressive treatment<sup>[12-18]</sup>.

In particular, for HBV and HCV infection, screening for the following serologic markers should be evaluated: antibody to hepatitis B core (anti-HBc), antibody to hepatitis B surface antigen (anti-HBsAg), hepatitis B surface antigen (HBsAg) and antibody to HCV (anti-HCV)<sup>[12,15,18,19]</sup>. In case of detection of one or more markers of HBV infection the patients must be evaluated for the presence of HBV DNA in the sera<sup>[20]</sup>. If anti-HCV serum is detected, HCV RNA should be searched for by a sensitive method<sup>[20]</sup>. The existence of either HBV or HCV infection or both in PsO patients eligible

for a systemic therapy poses a series of challenging problems. In particular, the administration of an immunosuppressive drug can alter the relationship between the host and the virus and worsen a coexisting chronic infection. Moreover, cDMARDs have different degrees of hepatic toxicity<sup>[9,11]</sup> therefore increasing the risk of worsening an already compromised liver as a consequence of the HBV or HCV infection.

PsO patients with infectious diseases such as HBV or HCV are excluded by the randomized controlled clinical trial. Therefore, data available on PsO patients with HBV or HCV infection, treated with systemic drugs, rely mainly on the reports of single cases or analyses of small groups of patients.

The aim of the present article is to describe how to manage and monitor PsO patients with HBV or HCV infection who need systemic antipsoriatic drugs.

## MONITORING AND MANAGEMENT OF PsO PATIENTS TREATED WITH cDMARDs OR bDMARDs AND CONCOMITANT HBV INFECTION

The first aspect to consider in patients with severe PsO and concomitant HBV infection, is to define the phase of the latter disease<sup>[18-20]</sup> and the degree of possible liver damage. To do so, a close collaboration between dermatologist and hepatologist is needed<sup>[18-20]</sup>.

As a rule, during the active phases of HBV infection, systemic anti-psoriatic therapies should be deferred. After an adequate control of infection, by means of anti HBV drugs is obtained<sup>[18-21]</sup>, therapies should be started. Active HBV infection includes different phases<sup>[22-24]</sup> not necessarily sequential, such as: (1) acute infection (defined as new-onset HBV infection that may or may not be icteric or symptomatic); and (2) chronic (defined as the persistence of HBsAg for six months or more) and encompassing different phases (immune-tolerant, HbeAg-positive immune-active, HBeAg-negative immune reactivation).

Acitretin is the only drug that could be administered during the active phases of HBV infection. However, the administration of said drug should be reserved only for selected cases without a severe impairment of liver function.

In daily clinical practice the more frequent scenarios that can be encountered are represented by patients with serological markers indicative of a previous exposure to HBV, with low or undetectable viral load. In particular, these subjects can be in one of the following infectious phases: (1) inactive HBV infection [serum HBV DNA < 2000 IU/mL, normal alanin aminotransferase (ALT) levels, HBsAg present, antibody to hepatitis B envelope antigen (anti-HBeAg)] present, minimal liver necroinflammation but variable fibrosis); (2) occult HBV infection (serum HBV DNA

< 200 IU/mL or undetectable, HbsAg negative, anti-HBc positive, anti-HBs negative); and (3) resolved HBV infection [(rHBV); anti-HBs positive ± anti-HBc]. Some confusion exists regarding the terms "occult carrier" and "rHBV". In fact, some Authors define as "occult carriers" (or "potential occult carriers") those patients who are indicated by other authors as rHBV and vice versa<sup>[22-27]</sup>. In this paper, the terms will be used following the above reported classification. The patients, whether inactive or occult carriers or with rHBV, can be at risk of HBV reactivation (defined as the sudden increase in HBV replication) after starting an immunosuppressive therapy<sup>[28]</sup>. As expected, the risk is significantly greater in the inactive carriers as compared to occult ones. Even more rare is the case of viral reactivation in rHBV<sup>[29]</sup>. The possible occurrence of one of the three previously mentioned infectious phases in a given PsO patient, raises some problems regarding their therapeutic management. In particular: (1) which drug can be safely administered? (2) which patients need anti HBV prophylaxis to prevent HBV reactivation? And (3) which serological markers should be monitored after an antipsoriatic therapy is started?

To answer these questions the cDMARDs and bDMARDs must be analyzed separately.

### cDMARDs

**Acitretin:** Acitretin administration is considered, due to its potential hepatotoxicity, a relative contraindication in hepatitis resulting from viral infections<sup>[18]</sup>. However, acitretin (preferably in association with ultraviolet B therapy) can be a possible option in those subjects without significant signs of liver damage as revealed by serological [ALT, aspartate transaminase (AST), gamma-glutamyl-transferase (GGT), bilirubin, alkaline phosphatase] and instrumental (ultrasonography, fibroscan) methods. Unfortunately, the effectiveness of acitretin as monotherapy and its side-effects (teratogenicity, mucosal dryness, hypertriglyceridemia) other than the potential hepatic toxicity<sup>[30]</sup> limits its use in many patients.

**Cyclosporin a:** The current dermatologic guidelines on the management of psoriatic disease do not give clear indications regarding the use of cyclosporin a (CyA) in patients with PsO and concomitant HBV infection<sup>[18]</sup>. The only reports of HBV reactivation concern severe immunosuppressed subjects such as renal transplant recipients and hematological patients<sup>[31,32]</sup>.

In a cohort of patients with rheumatoid arthritis (RA) who were anti-HBc positive and/or anti-HBs positive (defined by the Authors as resolved HBV infection) treated with either cDMARDs and or bDMARDs, CyA did not result associated with an activation of HBV infection<sup>[33]</sup>. However, the potential risks of HBV reactivation should not be underestimated also using the relatively low doses of CyA as those usually given to PsO patients. Lacking clear indications, and on the

**Table 2** Diagnosis and distribution of patients treated with tumor necrosis factor- $\alpha$  inhibitors according to the hepatitis B virus serological profile

Ref.	Diagnosis, <i>n</i>	Inactive carriers (HBsAg <sup>+</sup> ), <i>n</i>	Occult carriers or resolved HBV (anti-HBc <sup>+</sup> , anti-HBs <sup>-</sup> or anti-HBs <sup>±</sup> anti-HBc), <i>n</i>	Prophylaxis <sup>2</sup> , <i>n</i>	Reactivation, <i>n</i>
Charpin <i>et al</i> <sup>[42]</sup>	PsA, 5	0	5	0	0
Prestinari <i>et al</i> <sup>[43]</sup>	PsO, 1	0	1	0	0
Nosotti <i>et al</i> <sup>[44]</sup>	PsO, 4; PsA, 3	1	6	1 (Lamivudine)	0
Caporali <i>et al</i> <sup>[45]</sup>	PsA, 4	0	4	0	0
Kim <i>et al</i> <sup>[46]</sup>	PsA, 2	0	2	0	0
Fotadiou <i>et al</i> <sup>[47]</sup>	PsO, 7	7	0	7 (Lamivudine)	0
Prignano <i>et al</i> <sup>[48]</sup>	PsO, 12	0	12	0	0
Cassano <i>et al</i> <sup>[49]</sup>	PsO, 28; PsA, 34	0	62	0	0
Cho <i>et al</i> <sup>[50]</sup>	PsA, 2	2	0	0	1
Navarro <i>et al</i> <sup>[51]</sup>	PsO, 13	0	13	0	0
Laurenti <i>et al</i> <sup>[52]</sup>	PsA, 8	1	7	1 (Lamivudine)	0
Navarro <i>et al</i> <sup>[53]</sup>	PsO, 4	4	0	3 (Lamivudine); 1 (adefovir <sup>2</sup> entecavir)	0
<sup>1</sup> Sanz-Bueno <i>et al</i> <sup>[54]</sup>	PsO, 20	0	20	0	0

<sup>1</sup>This group also includes 6 patients who received UTK; <sup>2</sup>Only inactive carriers. PsO: Psoriasis; PsA: Psoriatic arthritis.

basis of our personal experience, we believe that CyA could be administered to patients who are HBV occult carriers or with rHBV if adequately monitored (see below).

**Methotrexate:** Data available on the use of methotrexate (MTX) in patients with HBV infection were gathered from patients with rheumatologic or inflammatory bowel disease<sup>[34,35]</sup>. Whether or not MTX can be safely administered to patients with a history of HBV infection is not clear<sup>[34,36]</sup>.

Basically, in the dermatological field, the different guidelines agree on avoiding MTX therapy in all patients whose seromarkers indicate an exposition to HBV<sup>[12,18,37]</sup>.

### bDMARDs

**TNF inhibitors:** There is evidence from experimental models that TNF plays a critical role in HBV clearance from infected hepatocytes<sup>[38]</sup>. Therefore, a detrimental effect is expected in terms of worsening or reactivation of HBV infection in subjects treated with TNF inhibitors (TNFis).

Over the past years several cases of HBV reactivation have been reported with either infliximab (IFX), adalimumab (ADA) or etanercept (ETA) therapy, mainly in patients with rheumatologic inflammatory diseases or inflammatory bowel disease<sup>[21,39,40]</sup>.

Whether or not different TNFis carry a different risk of HBV reactivation is currently not clear<sup>[41]</sup>. Some studies suggest a major risk of HBV reactivation for IFX as compared to other TNFis<sup>[21]</sup>.

Presently, literature data regarding the administration of TNFis in PsO or PsA subjects with concomitant HBV infection is available for 200 patients<sup>[42-56]</sup>. The majority of subjects reported are inactive or occult carriers, or with rHBV.

On the whole, patients were treated for a period ranging from 24 wk<sup>[43]</sup> to 6 years<sup>[52]</sup>. The TNFi more frequently administered was ETA, followed by ADA and finally IFX.

In Table 2 are summarized the cases of PsO and/or PsA grouped in: (1) inactive carriers; and (2) occult carriers or rHBV. The cases shown in Table 2, are limited to those for whom there was sufficient information in each report to permit their inclusion in one of the two above cited groups.

As shown in Table 2, none of the patients who were occult carriers or with rHBV experienced an HBV reactivation during TNFis therapy. None of the above cited subjects received antiviral prophylaxis.

Concerning patients who were inactive carriers, none of those who received antiviral prophylaxis experienced an HBV reactivation. On the contrary, HBV reactivation has been reported only in one case of an inactive carrier who did not receive antiviral prophylaxis (Table 2). In addition, two other patients of the same series with chronic HBV, who did not take prophylaxis, had viral reactivation<sup>[50]</sup>.

Regarding the use of TNFis in PsO with active HBV infection only one case has been reported so far<sup>[57]</sup>. Said subject received lamivudine therapy one month before starting IFX. This therapy was continued during treatment with TNFi for 6 mo with a significant improvement of PsO and a decrease of both viral load and transaminases. Thereafter, to obtain a better control of viral replication, lamivudine was substituted with entecavir and at the 9<sup>th</sup> month a further decrease of viral load was recorded, transaminases levels being within normal range and PsO under control.

**Ustekinumab:** Ustekinumab (UTK) is a fully human immunoglobulin G1k monoclonal antibody, anti-IL12p40, which binds to the shared p40 subunit of

**Table 3** Diagnosis and distribution of patients treated with ustekinumab according to the hepatitis B virus serological profile

Ref.	Diagnosis, <i>n</i>	Inactive carriers (HBsAg <sup>+</sup> ), <i>n</i>	Occult carriers or resolved HBV (anti-HBc <sup>+</sup> , anti-HBs <sup>-</sup> or anti-HBs <sup>±</sup> anti-HBc), <i>n</i>	Prophylaxis <sup>1</sup> , <i>n</i>	Reactivation, <i>n</i>
Navarro <i>et al</i> <sup>[53]</sup>	PsO 1	1	0	1 (Entecavir)	0
Chiu <i>et al</i> <sup>[60]</sup>	PsO 14	11 <sup>2</sup>	3	4 (Entecavir)	2
Hayashi <i>et al</i> <sup>[61]</sup>	PsO 5	0	5	0	0
Koskinas <i>et al</i> <sup>[62]</sup>	PsO 1	0	1	0	1
Steglich <i>et al</i> <sup>[63]</sup>	PsO 1	0	1	1 (Lamivudine)	0

<sup>1</sup>Only inactive carriers; <sup>2</sup>Six with diagnosis of chronic hepatitis. PsO: Psoriasis; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; Hbc: Hepatitis B core.

IL-12 and IL-23 with high affinity and specificity<sup>[8]</sup>. Because IL-12 plays a key role in triggering an effective cellular immune response directed towards the elimination of intracellular pathogens<sup>[58,59]</sup> its inhibition can contribute to HBV reactivation.

From 2013, 28 cases of PsO with concomitant HBV infection have been treated with UTK<sup>[53,54,60-62]</sup>. The duration of treatments ranged from 4 mo<sup>[60]</sup> to 3 years<sup>[63]</sup>.

In Table 3, 22 out of the 28 above cited patients are shown, since 6 subjects belong to the case series reported by Sanz-Bueno *et al*<sup>[54]</sup> and included in Table 2.

At present the lack of data does not permit us to draw any conclusions about the safety of UTK in patients with HBV infection.

However, as shown in Table 3, 2 of the 11 inactive carriers and one patient with rHBV experienced a reactivation of HBV infection after 4 mo, 7 mo and 16 wk, respectively<sup>[60,62]</sup>. Antiviral prophylaxis was not administered to said subjects.

### Antiviral prophylaxis

On the basis of the above reported data, it is clear that HBV infection does not represent a barrier to the administration of an immunosuppressive therapy in patients with severe PsO. However, when a patient is eligible to a long-lasting immunosuppressive therapy such as bDMARDs, the risk of HBV reactivation must be taken into account.

It is widely accepted that all subjects who are inactive carriers need an antiviral prophylaxis<sup>[10,38-40]</sup>. The latter should be started 2-4 wk before a bDMARD is given and continued for 6-12 mo after its suspension<sup>[10,38-40]</sup>. Concerning the type of antiviral drug to be administered, the American Gastroenterology Association (AGA) suggests a third generation nucleos(t)ide (entecavir or tenofovir) due to their high resistance to lamivudine<sup>[64]</sup>.

Whether or not patients who are occult carriers or with rHBV infection should receive antiviral prophylaxis is a debatable issue<sup>[10,38-40,64]</sup>. The recent AGA guidelines suggest administering antiviral prophylaxis also in patients who are HbsAg-negative/anti-HBc positive (whether or not anti-HBs positive) treated with either TNFis or UTK<sup>[64]</sup>. However, in the context of PsO treatment with bDMARDs patients do not

seem to carry a concrete risk of HBV reactivation. Therefore, in the above mentioned category of patients prophylaxis against HBV reactivation is probably not necessary<sup>[10,44]</sup>.

### Monitoring HBV reactivation

Regarding patients who are inactive carriers, considering the risk of HBV reactivation during therapy with a bDMARD, HBV DNA, ALT and AST, serum levels should be monitored monthly for the first 3 mo, then quarterly and continued after 6-12 mo of discontinuation of the aforementioned treatment<sup>[10,44]</sup>. More controversial is whether or not to measure HBV DNA serum levels in those PsO or PsA patients who are occult carriers or with rHBV treated with immunosuppressive drugs (CyA or bDMARDs)<sup>[10,40,44]</sup>. As already stated above, said patients do not seem to run a concrete risk of HBV reactivation. Moreover, the measurement of viral load is an expensive test. Therefore, occult carriers as well as patients with rHBV, can be monitored every 3 mo, checking for the presence in the serum of HBsAg in conjunction with the measurement of ALT and AST levels<sup>[10,44]</sup>. Monitoring should be continued with the same above cited timing after 6-12 mo from the discontinuation of the immunosuppressive therapy.

## MONITORING AND MANAGEMENT OF PsO PATIENTS TREATED WITH cDMARDs OR bDMARDs AND CONCOMITANT HCV INFECTION

After acute HCV infection occurs, from 15% to 25% of subjects spontaneously clear viremia while 75% to 85% of individuals develop chronic HCV infection<sup>[65]</sup>. The diagnosis of this last condition is based on the detection of both HCV antibodies and HCV RNA in the presence of signs of chronic hepatitis, either by elevated aminotransferases or by histology<sup>[66]</sup>. For the majority of patients the course of chronic HCV infections is benign. However, from 10% to 20% of subjects develop cirrhosis, generally in a time gap from 20 to 30 years<sup>[65]</sup>. It has been estimated that each year 1% to 4% of patients with HCV related cirrhosis will develop hepatocellular carcinoma (HCC), and 20%

will further progress to decompensated cirrhosis<sup>[65]</sup>.

In contrast to HVB, HCV reactivation is not very common<sup>[67]</sup>. However, when HCV reactivation occurs, its morbidity and mortality rates are similar to those of HBV reactivation<sup>[20]</sup>.

Concerning the treatment of PsO patients with concomitant HCV infection, a relatively limited number of data are available.

Among cDMARDs, acitretin and CyA could be two possible options while MTX is in general contraindicated for its substantial risk of hepatic toxicity<sup>[9,12,17,18]</sup>. Among bDMARDs, TNFis seems to be a relatively safe option (see below).

Very few data are at present available concerning the management with UTK of HCV infected patients since this biologic was introduced on the market several years after TNFis. Moreover, the use of UTK is presently approved only for PsO and PsA patients.

In the past, CyA has been considered by some Authors as third line as compared to TNFis in PsO subjects with HCV infection<sup>[67]</sup>.

However, several data indicate that both CyA and TNFis do not seem to cause different risks in worsening the chronic course of HCV infection<sup>[68-72]</sup>.

CyA and bDMARDs are probably the more frequently administered drugs for high-need PsO patients with concomitant HCV infection.

No data are currently available concerning the concomitant administration of systemic therapies for PsO and the new direct-acting antiviral medications approved for the treatment of chronic HCV infection.

In the following paragraphs treatment with CyA or bDMARDs of PsO patients with HCV infection are described.

### cDMARDs

**CyA:** Due to immunosuppressive activity, a detrimental effect of CyA in individuals with a chronic infection such as HCV, could be expected. However, experimental and clinical data indicate that CyA, in addition to its anti-inflammatory activity, can inhibit HCV viral replication<sup>[73]</sup>. In particular, this last effect has been found in patients carrying genotype 1 or 4 HCV<sup>[71,72]</sup>. However, also in patients carrying genotype 2, which is scarcely sensitive to antiviral effect of CyA, no worsening of HCV infection has been observed in spite of a favourable clinical course of their immunomediated diseases<sup>[72]</sup>. Said data clearly indicate that immunosuppressive and antiviral activity of CyA follow different pathways<sup>[73]</sup>.

Current available literature data on PsO patients with concomitant HCV infection treated with low dose of CyA include 11 patients, 7 of whom affected by PsA<sup>[69-72,74]</sup>. These patients received CyA for a period ranging from 16 to 38 mo and none experienced a worsening of their HCV infection. In some patients a lowering of HCV RNA serum levels has been reported<sup>[69]</sup>.

### bDMARDs

**TNFis:** Data available concerning the management with TNFis of PsO patients with HCV infection are increasing.

TNF- $\alpha$  is a key cytokine in stimulating immunomediated response to infections, especially against intracellular pathogens. Therefore, after inhibition of TNF- $\alpha$ , a worsening of a viral infection such as HCV could be expected. However, experimental and clinical data suggest that increased levels of TNF- $\alpha$  can have a detrimental effect on HCV infection<sup>[75-77]</sup>. In particular, the aforementioned cytokine seems to reduce cell capability to respond to interferon (IFN) signalling and, consequently, impair viral clearance<sup>[76]</sup>. Moreover, a direct correlation between elevated levels of TNF- $\alpha$  and those of ALT has been reported, with increased TNF- $\alpha$  levels having more severe histological activity<sup>[75,77]</sup>. A further indication that decreasing TNF- $\alpha$  concentrations can play a favourable effect on HCV infection comes from a study in which etanercept was administered as adjuvant to IFN and ribavirin in a group of HCV infected patients<sup>[78]</sup>. These subjects showed a higher decline of viral load and ALT as compared to the placebo group.

In addition to the data above reported, further observations indicate that TNFis can be safely administered to patients with different immune-mediated diseases and concomitant HCV infection<sup>[39,40,79]</sup>. In particular, in most of said patients viral load remained stable or decreased<sup>[39,40,79]</sup>. Serum HCV RNA increase > 1 log above baseline was rarely recorded and could not be confidently attributed to TNFis.

At present, 45 PsO and 33 PsA patients with concomitant HCV infection have been treated with TNFis<sup>[48,53,80-106]</sup>. Diagnosis, ALT and viral load outcomes at the last follow-up of the mentioned subjects are shown in Table 4. Of all the patients reported, 66 received a single TNFi (56 ETA, 9 ADA, 1 IFX). Six patients were treated sequentially with 2 TNFis (1 with IFX and then ADA, 4 with ETA and then ADA and 1 with ETA and then IFX). One patient was treated sequentially with 3 TNFis (ETA followed by IFX and then ADA).

The duration of TNFis was highly variable ranging from 1 to 48 mo<sup>[97,105]</sup>.

At baseline, liver biopsy specimens were available from 16 patients which revealed various grades of fibrosis ranging from F0 to F4<sup>[81-85,87,95,96,99,101-103]</sup>. Of said subjects only 2 underwent a second liver biopsy control which showed no significant histological changes compared to pretreatment findings<sup>[95]</sup>.

As shown in Table 4, in the majority of the patients described, ALT and HCV RNA viral load remained unchanged or declined during TNFis therapy.

On the whole, the safety profile of TNFis appears to be reasonably good in PsO patients with concomitant HCV infection even if 4 cases of hepatocellular carcinoma (HCC) were recorded<sup>[53,105]</sup>. However, 3 out of

**Table 4** Diagnosis and laboratory characteristics of reported psoriatic patients with chronic hepatitis B virus infection treated with tumor necrosis factor- $\alpha$  inhibitors

Ref.	Diagnosis, <i>n</i>	Concomitant HCV therapy, <i>n</i>	ALT outcomes at last follow-up compared to baseline, <i>n</i>	HCV viral load outcome at last follow-up compared to baseline, <i>n</i>
Khanna <i>et al</i> <sup>[80]</sup>	PsA, 1	1 (N/A)	1 (N/A)	1 (N/A)
Magliocco <i>et al</i> <sup>[81]</sup>	PsA, 3	0	3 (=)	2 (↓); 1 (N/A)
Cecchi <i>et al</i> <sup>[82]</sup>	PsO, 1	0	1 (=)	1 (=)
De Simone <i>et al</i> <sup>[83]</sup>	PsO, 2	0	2 (=)	2 (↓)
Asladinis <i>et al</i> <sup>[84]</sup>	PsA, 1	0	1 (=)	1 (↓)
Rokshar <i>et al</i> <sup>[85]</sup>	PsO, 1	0	1 (N/A)	1 (=)
Pitarch <i>et al</i> <sup>[86]</sup>	PsA, 1	1 (N/A)	1 (=)	1 (N/A)
Linadarki <i>et al</i> <sup>[87]</sup>	PsA, 1	0	1 (=)	1 (=)
Alcaide <i>et al</i> <sup>[88]</sup>	PsO, 1	0	1 (=)	1 (=)
Piccolo <i>et al</i> <sup>[89]</sup>	PsO, 1	0	1 (↑)	1 (↓)
Collazzo <i>et al</i> <sup>[90]</sup>	PsO, 1	0	1 (=)	1 (N/A)
Cassano <i>et al</i> <sup>[91]</sup>	PsO, 1	0	1 (=)	1 (=)
Cavazzana <i>et al</i> <sup>[92]</sup>	PsA, 1	0	1 (=)	1 (=)
Behnam <i>et al</i> <sup>[93]</sup>	PsO, 1	1 (IFN + Rib)	1 (↓)	1 (↓)
Ventura <i>et al</i> <sup>[94]</sup>	PsO, 1; PsA, 1	0	2 (↓)	1 (↑); 1 (↓)
Paradisi <i>et al</i> <sup>[95]</sup>	PsA, 2	0	2 (=)	2 (=)
Prignano <i>et al</i> <sup>[96]</sup>	PsO, 1	0	1 (N/A)	1 (=)
Richetta <i>et al</i> <sup>[97]</sup>	PsO, 1 <sup>1</sup>	0	1 (N/A)	1 (N/A)
Garavaglia <i>et al</i> <sup>[98]</sup>	PsO, 3; PsA, 2	1 (IFN + Rib)	1 (=); 4 (↓)	3 (=); 1 (↓)
Gandhi <i>et al</i> <sup>[99]</sup>	PsO, 1	0	1 (↓)	1 (↓)
Di Lernia <i>et al</i> <sup>[100]</sup>	PsO, 1 <sup>3</sup>	0	1 (=)	1 (=)
Zanni <i>et al</i> <sup>[101]</sup>	PsA, 3	0	3 (=) <sup>4</sup>	3 (=)
Prignano <i>et al</i> <sup>[48]</sup>	PsO, 6	0	6 (=)	6 (=)
Mederacke <i>et al</i> <sup>[102]</sup>	PsA, 1	1 (IFN + Rib)	1 (N/A)	1 (↓)
Navarro <i>et al</i> <sup>[53]</sup>	PsO, 20 <sup>2</sup>	3 (IFN + Rib)	See references	See references
Bartalesi <i>et al</i> <sup>[103]</sup>	PsO, 1	1 (IFN + Rib)	1 (↓)	1 (↓)
Costa L <i>et al</i> <sup>[104]</sup>	PsA, 15	0	13 (=); 2 (↓)	14 (=); 1 (↓)
Di Nuzzo <i>et al</i> <sup>[105]</sup>	PsA, 2	1 (IFN + Rib)	1 (=); 1 (↓)	2 (↓)
Salvi <i>et al</i> <sup>[106]</sup>	PsO, 1	0	1 (↑)	1 (=)

<sup>1</sup>1 erythrodermic psoriasis; <sup>2</sup>1 erythrodermic psoriasis, 2 palmoplantar psoriasis; <sup>3</sup>1 palmoplantar psoriasis; <sup>4</sup>1 patient with concomitant alcoholic hepatitis. PsO: Psoriasis; PsA: Psoriatic arthritis; =: No significant change; ↓: Decreased; ↑: Increased; N/A: Not available; IFN: Interferon; Rib: Ribavirine.

4 said patients were affected by cirrhosis and it is impossible to draw any conclusion regarding a possible role of TNF inhibition in the appearance of the above cited HCC.

**UTK:** Concerning IL 12 and IL 23, both targeted by UTK, little is known about their activity in HCV infection. Presently available data suggest that IL-12 can have a relevant role against HCV in either acute or chronic phases of infection<sup>[57,107,108]</sup>.

At present, seven patients with PsO and HCV infection have been treated with UTK. Abuchar *et al*<sup>[109]</sup> in 2013, described the case of one patient with erythrodermic PsO and HCV infection who, after 2 mo of UTK therapy, experienced a very good response regarding his PsO without worsening of HCV infection.

Chiu *et al*<sup>[60]</sup> reported their experience on 4 PsO patients with HCV infection who received UTK for a period ranging from 5 to 11 mo. During the follow-up period, HCV viral copy numbers increased in 3 cases with only one subject meeting the criterion of HCV reactivation, recorded after 1 mo of UTK therapy. This last patient, who at baseline had a diagnosis of cirrhosis and previous HCC experienced a recurrence of HCC after 4 mo of UTK treatment.

Navarro *et al*<sup>[53]</sup>, in a study published in 2013, reported that two PsO patients with concomitant HCV infection received UTK for 16 and 12 mo, respectively. The first patient, at the end of follow-up, showed a decrease of viral load and slight increase of both ALT and AST. In the second patient at the end of follow-up, viral load remained unchanged with a slight decrease of both ALT and AST serum levels.

More data are needed to better define whether or not UTK can have a role in the treatment of PsO patients with HCV infection.

### Monitoring and managing of HCV infection

No guidelines are currently available on how to monitor PsO patients with HCV infection during treatment with CyA or bDMARDs.

Monitoring liver function tests (ALT, AST, alkaline phosphatase, bilirubin, albumin and platelet) and HCV-RNA load every 3-6 mo could be a valuable option for the majority of the patients.

However, it is important to point out that an optimal follow-up of the above-cited patients requires a strict collaboration with a consultant hepatologist. This latter will decide the timing of instrumental examinations, whether or not to perform a liver biopsy and whether

or not to offer a prophylactic anti-viral treatment.

## CONCLUSION

HBV and HCV are the pathogens which more frequently cause chronic hepatitis<sup>[110]</sup>.

Only few studies have evaluated the prevalence of the above-cited infectious disease in the PsO population. In 2011, Yang *et al.*<sup>[111]</sup> reported an increased prevalence of HBV and HCV in PsO Taiwanese patients. In 2010, Cohen *et al.*<sup>[112]</sup> in their study performed in Israel found an increased prevalence of HBC but not of HBV in PsO compared to control. The different frequency of HBV and HCV infection, as well as of PsO worldwide, can account for the discrepancies among the data published so far.

The chance to encounter in clinical practice PsO patients in high need of treatment who are HBV or HCV infected, should not be underestimated. Concerning said issue all current guidelines recommend screening PsO patients eligible for an immunosuppressive therapy due to the presence of HBV and HCV infection. However, no guidelines presently available give indications on how to manage and monitor these patients. Notwithstanding the above-cited limitations, immunosuppressive therapies should not be an insurmountable barrier for subjects with severe PsO and concomitant chronic HBV or HCV infection.

As already stated in this paper, it is essential that the aforementioned patients be referred to a hepatologist for expert clinical management.

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