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Observational Study

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Abstract

AIM
To evaluate the outcomes in biological treatment and quality of life of psoriatic patients with chronic hepatitis C (CHC) treated with new Direct-Acting Antiviral agents (DAAs) compared to pegylated interferon-2α plus ribavirin (P/R) therapy.

METHODS
This is a retrospective study involving psoriatic patients in biological therapy who underwent anti-hepatitis C virus (HCV) treatment at the Department of Dermatology Galeazzi Orthopaedic Institute Milan, Italy from January 2010 to November 2017. The patients were divided into two groups: patients that underwent treatment with DAAs and patients that underwent HCV treatment with P/R. Patients were assessed by a dermatologist for psoriasis symptoms, collecting Psoriasis Area Severity Index (PASI) scores and the Dermatology Quality of Life Index (DLQI). PASI and DLQI scores were evaluated 24 wk after the end of HCV treatment and were assumed as an outcome of the progression of psoriasis. Switching to a different bDMARD was considered as an inadequate response to biological therapy. The dropout of HCV therapy and sustained virological response (SVR) were considered as outcomes of HCV therapy.

RESULTS
Fifty-nine psoriatic patients in biological therapy underwent antiviral therapy for CHC. Of this, 27 patients were treated with DAAs and 32 with P/R. After 24 wk post treatment, the DLQI and the PASI scores were significantly lower (P < 0.001 and P < 0.005, respectively) in the DAAs group compared with P/R group. None of the patients in the DAAs group (0/27) compared to 8 patients of the P/R group (8/32) needed a shift in biological treatment.

CONCLUSION
DAAs seem to be more effective and safe than P/R in HCV-positive psoriatic patients on biological treatment. Fewer dermatological adverse events may be due to interferon-free therapy.

Key words: Hepatitis C virus; New Direct-Acting Antiviral agents; Psoriasis; Biological disease modifying drugs

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The present study is a spin-off observational retrospective study on HCV psoriatic patients, resulting as re-analysis of a previous study towards the re-circulation of CD4+ memory T-cells in psoriatic patients, approved by the Institutional Review Board (Comitato Etico dell’Ospedale San Raffaele, Milano)\(^{[11]}\). This previous study had as exclusion criterion the absence of acute and chronic systemic or cutaneous infections during sample collection. Psoriasis diagnosis was performed by a Dermatologist following the Psoriasis Italian Guidelines\(^{[10]}\), and the diagnosis of CHC according the WHO guidelines\(^{[14]}\).

Inclusion criteria

Inclusion criteria were age > 18 years old, signed consent forms, no previous transplantation, no pregnancy, no hereditary hepatic diseases, no drug addiction, and no alcohol abusers [Alcohol Use Disorders Identification Test (AUDIT) score < 7], negative results at screening tuberculosis, absence of acute and chronic systemic or cutaneous infections during sample collection. Psoriasis diagnosis was performed by a Dermatologist following the Psoriasis Italian Guidelines\(^{[10]}\), and the diagnosis of CHC according the WHO guidelines\(^{[14]}\).

Exclusion criteria

Exclusion criteria were age < 18 years old, pregnancy, drug addiction, alcohol abusers [Alcohol Use Disorders Identification Test (AUDIT) score > 7], HIV infection.

Outcomes of the study

PASI, DLQI were evaluated 24 wk after the end of HCV treatment (T1) and were assumed as an outcome of the progression of psoriasis. Switching to a different bDMARD was considered as inadequate responses to biological therapy. The dropout of HCV therapy, and sustained virological response (SVR) were considered as outcomes of HCV therapy.

Data collection and variables definitions

Baseline clinical characteristics, medical history, biochemical variables, and pharmacologic treatments employed during hospitalization were retrospectively collected and recorded on a computer database. SVR was defined as a confirmed undetectable serum HCV-RNA level 24 wk after the discontinuation of HCV therapy. Patients not fulfilling the SVR definition criteria were classified as non-SVR.

Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables are presented as absolute values and percentages. Comparisons between continuous variables were performed using Mann–Whitney or Kruskall–Wallis tests and comparisons between categorical variables were performed using the \(\chi^2\) or Fisher’s exact test. Statistical significance was defined as \(P < 0.05\). Data analysis was performed using statistical software R-version 3.2.4.

RESULTS

A total of 59 psoriatic patients met the inclusion criteria (27 in the DAA-group and 32 in the P/R-group) and were included in this analysis. The patients’ main characteristics are summarized in Table 1. All the patients in the P/R-group were treated with pegylated interferon-2\(\alpha\) plus ribavirin; in the DAA-group 25 patients (92.6%) were treated with Sofosbuvir plus Daclatasvir, 1 patient was treated with Sofosbuvir + ribavirin: 1 (3.7%) and 1 patient (3.7%) was treated with Sofosbuvir plus simeprevir plus ribavirin. The median age was 56.7 ±
8.9 years in the DAA-group and 58.2 ± 6.7 years in the P/R-group, respectively; 66.7% patients were men in the DAA-group and 75% patients were men in the P/R-group, respectively. The median body mass index (BMI) was 24.3 ± 2.41 in the DAA-group and 25 ± 1.86 in the P/R-group, respectively. The median psoriasis duration was 21.5 ± 8.6 years in the DAA-group and 18 ± 6.7 years in the P/R-group, respectively. In the DAA-group the bDMARD used, was Etanercept, Adalimumab, Ustekinumab and Secukinumab in 12 (44.4%), 9 (33.3%), 5 (18.5%), and 1 (0.04%) patients, respectively; in the P/R-group the bDMARD used, was Etanercept, Adalimumab and Ustekinumab in 15 (46.9%), 2 (7.4%) and 5 (18.5%) patients, respectively. Switching among biologic therapies, before hepatitis C treatment, was 1.2 ± 0.3 in DAA-group and 1.5 ± 0.5 in P/R-group. Two patients (7.4%) of the DAA-group and 3 patients (9.4%) of the P/R-group presented psoriatic arthritis, respectively. In the DAA-group the HCV genotypes were 1, 2 and 4 in 21 (77.8%), 10 (31.3%) and 6 (21.9%) patients, respectively. In the P/R-group the HCV genotypes were 1, 2 and 3 in 17 (53.1%), 9 (28.1%) and 5 (15.6%) patients respectively. The MELD score was 9.3 ± 2.5 in DAA-group and 6.5 ± 0.8 in the P/R-group, respectively. The viral load at the baseline was 6.2 log_{10} ± 5.7 log_{10} UI/mL in the DAA-group and 6.1 log_{10} ± 6.0 log_{10} UI/mL in the P/R-group, respectively. All the 27 patients (100%) in the DAA-group obtained SVR, whereas only 37.5% (12/32) of patients in the P/R-group achieved a SVR. Two out of 27 patients of DAA-group had autoimmune comorbidities: 1 (3.7%) rheumatic arthritis and 1 (3.7%) systemic erythematosus lupus; 1 (3.1%) out of 32 patients of P/R-group had autoimmune comorbidity: ankylosing spondylitis. In the DAA-group other comorbidities were cardiovascular diseases, metabolic syndrome, chronic obstructive disease, and HBV in 6 (22.2%), 2 (7.4%), 5 (18.5%), 1 (3.7%) patients, respectively. In the P/R-group other comorbidities were cardiovascular diseases, metabolic syndrome, chronic obstructive disease, and HBV in 3 (9.4%), 1 (3.1%), 2 (6.3%), 1 (3.1%) patients, respectively. None of the 59 psoriatic patients enrolled in the study had renal insufficiency.

The comparison between the patient scores and laboratories findings according to HCV eradication treatment is shown in Table 2: There were no differences in PASI scores between the 2 HCV treatment groups; after 24 wk to the end of the HCV treatment there

| HCV Genotype, n (%) | 1 | 2 | 3 | 4 | 5/6 |
|---------------------|---|---|---|---|-----|
| 1                   | 21 (77.8) | 5 (18.5) | 1 (3.1) | - | - |
| 2                   | 5 (18.5) | - | 2 (6.3) | - | - |
| 3                   | 1 (3.7) | - | 1 (3.1) | - | - |
| 4                   | - | - | 1 (3.1) | - | - |
| 5/6                 | - | - | - | 2 (6.3) | - |

| MELD score | DAA-group | P/R-group |
|------------|------------|------------|
|            | 9.3 ± 2.5  | 6.5 ± 0.8  |

| HCV viral load (T0), IU/mL, mean ± SD | DAA-group | P/R-group |
|--------------------------------------|------------|------------|
|                                      | 6.2 log_{10} ± 5.7 log_{10} | 6.1 log_{10} ± 6.0 log_{10} |

| SVR, n (%) | 27/27 (100) | 12/32 (37.5) |
|------------|-------------|--------------|

| Autoimmune comorbidities, n (%)      | DAA-group | P/R-group |
|--------------------------------------|------------|------------|
| Rheumatic arthritis                   | 1 (3.7)    | -           |
| Ankylosing spondylitis                | -          | 1 (3.1)    |
| Systemic erythematosus lupus          | 1 (3.7)    | -           |

| Other comorbidities, n (%)           | DAA-group | P/R-group |
|--------------------------------------|------------|------------|
| Cardiovascular disease               | 6 (22.2)   | 3 (9.4)    |
| Metabolic syndrome                   | 2 (7.4)    | 1 (3.1)    |
| COPD                                 | 5 (18.5)   | 2 (6.3)    |
| Renal insufficiency                  | 0 (0)      | 0 (0)      |
| HBV                                  | 1 (3.7)    | 1 (3.1)    |

Categorical variables are expressed as n (%). Numeric variables are expressed as median and SD. BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; DAA: New Direct-Acting Antiviral agent; HBV: Hepatitis B virus; HCV: Hepatitis C virus; P/R: Pegylated interferon-2α plus ribavirin; MELD: Model for end-stage liver disease; SVR: Sustained virological response.
was a significant reduction of PASI score in DAA-group when compared to P/R-group patients \( (P < 0.005) \). Patients in the P/R-group (8 patients, 25%) need a significantly \( (P < 0.001) \) frequent change of biological treatment compared to DAA-group (no patients). There was no difference in the use of topical treatments in the 2 groups at baseline (100% in both groups) and after 24 wk to the end of the HCV treatment (100% in both groups). Although there was no difference in the DLQI at the beginning of the treatment in the 2 groups, after 24 wk the DLQI was significantly improved in the DAA-group when compared to P/R-group patients \( (P < 0.001) \). HCV treatment was significantly better tolerated \( (P < 0.005) \) by DAA-group patients with no dropout; 9 out of 32 P/R-group patients (28.1%) dropped out of HCV treatment. HCV eradication was significantly higher \( (P < 0.005) \) in DAA-group compared to P/R-group: SVR was obtained in 100% (27/27) of patients treated with DAA group vs 80% (24/30) of patients treated with P/R group. The flare usually occurs one to 6 wk after starting interferon-α and may lead to its discontinuation \([20]\).

There appears to be an intricate relationship between psoriasis and HCV infection as seen in previous reports. HCV in predisposed individuals upregulates cathelecidin, Toll like receptor 9 (TLR-9) and interferon (IFN)-γ which are all involved in the development of psoriasis plaques. Pegylated interferon may also initiate and maintain psoriasis inflammation by activating Th1 and Th17 via myeloid DCs \([7,21]\). Cathelecidin bonds self-DNA. It is released after various injury stimuli via TLR-9 plasmacytoid and DCs to produce type 1 interferons (α/β), which drives T-cell polarization towards Th1 and Th17 via myeloid DCs. This initiates the trigger and further maintenance of psoriasis \([16]\). Likewise, pegylated interferon may act directly via myeloid resident DCs on Th1 cells and also on Th17 cells at the same time by increasing their activation and release of IL-17. IL-17 is a chemo-attractant for neutrophils to the skin and IL-22 causes keratinocyte hyperproliferation \([21]\). Despite these preliminary hypotheses, data regarding the association of HCV and psoriasis remain unclear and a matter of quality of life and in eradication of HCV. Patients with a worse prognosis treated with P/R could be attributed to two possible causes: (1) Interferon “itself” has dermatological side effects \([15]\), worsening psoriasis and (2) DAAs are more effective than interferon-based therapy increasing the rates of SVR (even up to 100%) \([16]\), suggesting that HCV could promote psoriatic disease. Eradication treatment of HCV with interferon has been described as the drug that can induce de novo psoriasis or flares in psoriatic patients \([17-19]\). The flare usually occurs one to 6 wk after starting interferon-α and may lead to its discontinuation \([20]\).

**DISCUSSION**

In our study, psoriatic patients of the DAA-group had a better prognosis compared to the P/R-group, both in progression of psoriasis (and consequent worsening of

### Table 2  Levels of sIL-2R, ALT, and HBV DNA in the sera of patients with chronic hepatitis B virus infection (mean ± SD)

| DAA-group |  |  |  |
|---|---|---|---|
| PASI (T0), mean ± SD | 11.6 ± 5.2 | 9.4 ± 3.5 |  |
| PASI (T1), mean ± SD | 5.2 ± 1.6 | 8.3 ± 4.5 | < 0.005 |
| Biological treatment shifts, n (%) | - | 8 (25) | < 0.001 |
| Topical treatments (T0), n (%) | 27 (100) | 32 (100) | - |
| Topical treatments (T1), n (%) | 27 (100) | 32 (100) | - |
| DLQI (T0), mean ± SD | 13 ± 2.3 | 12 ± 3.1 | - |
| DLQI (T1), mean ± SD | 11.2 ± 2.3 | - | < 0.001 |
| HCV treatment details, n (%) | Sofosbuvir + daclatasvir: 25 (92.6) | Pegylated-interferon-2a + ribavirin | - |
| Laboratory tests, mean ± SD |  |  |  |
| T0 | ALT | 45.6 ± 16.5 | 43 ± 9.2 | - |
| | AST | 54.6 ± 5.51 | 52.4 ± 12.5 | - |
| | GGT | 42.0 ± 13.59 | 43.3 ± 14.6 | - |
| T1 | ALT | 42.21 ± 12.4 | 43 ± 8.5 | - |
| | AST | 51.3 ± 4.2 | 51.9 ± 8.9 | - |
| | GGT | 40.8 ± 12.2 | 42.9 ± 14.1 | - |
| Dropout HCV-treatment, n (%) | 0/27 (0) | 9/32 (28.1) | < 0.005 |
| SVR, n (%) | 27/27 (100) | 12/32 (37.5) | < 0.005 |

Categorical variables are expressed as n (%), and compared by χ² or Fisher’s exact test. Numeric variables are expressed as median and SD, and compared by Mann-Whitney or Kruskall-Wallis tests. Statistical significance was considered as a P-value of < 0.05. DAA: New Direct-Acting Antiviral Agent; P/R: Pegylated interferon-2a plus ribavirin; PASI: Psoriasis Area Severity Index; T0: Baseline time (before starting the hepatitis C eradication treatment); T1: Six months after the end of hepatitis C eradication treatment; DLQI: Dermatology Quality of Life Index; HCV: Hepatitis C virus; SVR: Sustained virological response; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase.
debate. Some studies show no association while others show an increased prevalence of psoriasis among HCV-patients as reported by Cohen. Furthermore, limited data is present in literature regarding psoriasis induction and exacerbation due to interferon in HCV-psoriatic patients.

Experimental studies have shown that an intradermal injection of INF-γ, both on the non-lesional psoriatic and healthy skin, causes an elevation of inflammatory products such as TNF, IL-23 and inducible nitric oxide synthase which are characteristic of psoriatic plaques. An association between HCV infection and psoriasis has been suggested. The prevalence of HCV in psoriatic patients was increased compared to controls (1.03% vs 0.56%; P < 0.001). In a single center cross-sectional study conducted in a Japanese university hospital, the frequency of HCV infection was significantly higher in psoriatic (7.5%) than in non psoriatic patients (3.3%) in overall ages. Interestingly, when stratified by age at the first visit, HCV infection frequency was significantly higher in patients with psoriasis than in controls aged over 60 years (11.8% vs 6.6%, respectively, P = 0.0215) and 70 s (19.5% vs 7.3%, P < 0.0001). Psoriatic patients with CHC were significantly older at onset than non psoriatic CHC patients (median, 54 vs 39 years). There was also a stronger male predominance (male/female ratio, 4.4:1), similar family history of psoriasis, higher association of diabetes mellitus and hypertension, and significantly lower body mass index, in an age-stratified (> 40 years) analysis. Psoriatic patients with CHC were less obese, but still had a higher frequency of diabetes mellitus and hypertension. The authors hypothesized that psoriasis and HCV have pathophysiological factors in common with both mediated by proinflammatory cytokine tumor necrosis factor (TNF-α). In HCV infection, continuous inflammation mediated by TNF-α leads to liver cirrhosis and diabetes mellitus. The link between psoriasis and HCV infection has been shown experimentally in a recent study of Chun et al; the authors performed two 2 mm punch biopsies of lesional and nonlesional skin in 10 patients who were HCV-negative psoriatic and 7 HCV-positive psoriatic patients. The biopsies were used to measure cathelicidin, TLR9 and IFNc mRNA expression by quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR). The mRNA expression was calculated relative to the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and demonstrated that the cutaneous levels of inflammatory genes in HCV positive psoriatic patients are higher than the levels in patients with only psoriasis. The increased cutaneous levels of cathelicidin, TLR9 and IFNc of HCV-positive psoriatic patients as compared to HCV-negative psoriatics suggest that HCV infection may predispose patients to developing psoriasis. These findings seem to be confirmed clinically due to the worse prognosis of psoriasis in HCV-positive patients. The mean PASI score is significantly higher in cohorts of patients affected with hepatitis C than those with psoriasis alone.

In line with previous studies, our study confirmed that bDMARDs are safe in psoriatic patients with HCV infection. Literature bDMARDs are safe either in psoriatic patients with HCV infection and past HBV infection. Patients in the DAA-group had a significantly better response to bDMARDs compared to P/R-group, requiring a smaller transition to different bDMARDs. This may be due to a more favorable outcome in psoriasis (due to interferon-free therapy and greater HCV eradication), but also due to intrinsic DAs action. Immune reconstitution occurs in patients with whom HCV was successfully eradicated via DAs therapy. Restoration of the CD4+ T-cell compartment in the peripheral blood and a re-differentiation of the T lymphocyte memory compartment resulted in a more effector memory T cell population and a reduction in expression of the co-inhibitory molecule TIGIT in bulk T lymphocytes. Burchill et al showed a partial reversal of the exhausted phenotype in HCV-specific CD8+ T cells and a dampening of the activation state in peripheral NK cells. Spaan et al showed that viral load decline, as a consequence of DAs therapy in patients with chronic hepatitis C infection, reduces serum levels of NK cell-stimulating cytokines and causes correction of the altered NK cell phenotype observed in chronic HCV patients. CHC is characterised by innate immune activation with increased interferon-stimulated gene expression and by an altered phenotype of interferon-responsive natural NK cells. DAs treatment could improve the pro-inflammatory status due both to psoriasis and to the HCV infection making bDMARDs actions more effective.

The current study contains some limitations that need to be taken into account. This is a retrospective observational study conducted in a single Italian centre, thus our conclusions should be interpreted with caution and cannot be generalized to all HCV-positive psoriatic patients. In particular, a general under-reporting of toxicity, as with all observational studies, is possible. Another limitation is the small sample size and the relatively short follow-up. This is the first study to compare DAs to P/R for the management of HCV-positive psoriatic patients and unmeasured confounding variables could influence our findings. Thus, larger series with long-term follow-up are required to confirm this preliminary data.

In conclusion, new DAs are more effective than P/R in the eradication of HCV and the control of symptoms in psoriatic patients with CHC. Future studies are needed to evaluate the effects of DAs in this clinical setting, which may further aid in elucidating the etiologic and pathogenetic mechanism of psoriasis.

**ARTICLE HIGHLIGHTS**

**Research background**

Up to 0.06% of people suffer from both psoriasis and hepatitis C virus (HCV). Psoriatic patients with HCV are excluded by randomized controlled clinical trials.
Research motivation
No data is currently available concerning the concomitant administration of biological drugs and the medications approved for the treatment of HCV infection, as new Direct-Acting Antiviral agents (DAAs).

Research objectives
Evaluate the outcomes in biological treatment and quality of life of psoriatic patients with chronic hepatitis C (CHC) treated with new DAAs compared to pegylated interferon-2α plus ribavirin (P/R) therapy.

Research methods
Psoriatic patients, in biological therapy, who underwent anti-HCV treatment were retrospectively reviewed. The patients were divided into two groups: patients that underwent therapy with DAAs and patients that underwent HCV treatment with P/R. Patients were assessed for Psoriasis Area Severity Index (PASI) scores and the Dermatology Quality of Life Index (DLQI) switching to a different bDMARD, dropout of HCV therapy and sustained virolological response (SVR).

Research results
Twenty-seven patients were treated with DAAs and thirty-two with P/R. At three months, after completion of antiviral therapy, the DLQI and the PASI scores were significantly lower (P < 0.01 and P < 0.05, respectively) in DAAs group compared with P/R group. None of the patients in the DAAs group compared to the eight patients of the P/R group needed a change in biological treatment.

Research conclusions
DAAs seem to be more effective and safe than P/R in HCV-positive psoriatic patients on biological treatment.

Research perspectives
This is the first study which evaluated the HCV treatment of psoriatic patients on biological agents. Further studies are needed to evaluate the effects of DAAs in this clinical setting, which may further aid in elucidating the etiologic and pathogenetic mechanism of psoriasis.

REFERENCES
1. Boechcke WH, Schön MP. Psoriasis. Lancet 2015; 386: 983-994 [PMID: 26025581 DOI: 10.1016/S0140-6736(14)61909-7]
2. Psoriasis. Media resources of the American Academy of Dermatology. Available from: URL: https://www.aad.org/media/stats/conditions/psoriasis
3. Hepatitis C. Media centre of the World Health Organization; updated October 2017. Available from: URL: http://www.who.int/mediacentre/factsheets/facts164/en/
4. Viral Hepatitis. Division of Viral Hepatitis and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention of the Centers for Disease Control and Prevention; updated: May 11, 2017. Available from: URL: https://www.cdc.gov/hepatitis/statistics/index.htm
5. Huerta C, Rivero E, Rodriguez LA. Incidence and risk factors for psoriasis in the general population. Arch Dermatol 2007; 143: 1559-1565 [PMID: 18087008 DOI: 10.1001/archderm.143.12.1559]
6. Lande R, Botti E, Jandus C, Dojcinovic D, Fanelli G, Conrad C, Chamilos G, Feldmeyer L, Mariani B, Chon S, Vence L, Ricicri V, Guillaume P, Navarrini AA, Romero P, Costanzo A, Piccolaella E, Gilliet M, Frasca L, Corrighendum: the antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun 2015; 6: 6595 [PMID: 25759123 DOI: 10.1038/ncomms5795]
7. Chun K, Afshar M, Audish D, Kabibling F, Paik A, Gallo R, Hata T. Hepatitis C may enhance key amplifiers of psoriasis. J Eur Acad Dermatol Venereol 2017; 31: 672-678 [PMID: 27184185 DOI: 10.1111/jdv.13578]
8. Cohen AD, Weitzman D, Birkenfeld S, Dreier J. Psoriasis associated with hepatitis C but not with hepatitis B. Dermatology 2010; 220: 218-222 [PMID: 20185894 DOI: 10.1159/000286131]
9. Bonifati C, Lora V, Graceffa D, Nosotti L. Management of psoriasis patients with hepatitis B or hepatitis C virus infection. World J Gastroenterol 2016; 22: 6444-6455 [PMID: 27605880 DOI: 10.3748/wjg.v22.i28.6444]
10. Giosondi P, Altomare G, Ayala F, Bardazzì F, Bianchi L, Chiricozzi A, Costanzo A, Conti A, Davapo P, De Simone C, Fofi C, Naddi L, Offidani A, Parodi A, Piaserico S, Prigiano F, Rongiolfetti F, Stingeni L, Talamonti M, Girolomoni G. Italian guidelines on the systemic treatments of moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol 2017; 31: 774-790 [PMID: 28244153 DOI: 10.1111/jdv.14114]
11. Diani M, Galasso M, Cozzi C, Sgambelluri F, Altomare A, Cigni C, Frigerio E, Drago L, Volinia S, Granucci F, Altomare G, Realì E. Blood to skin recirculation of CD4+ memory T cells associates with cutaneous and systemic manifestations of psoriatic disease. Clin Immunol 2017; 180: 84-94 [PMID: 28392462 DOI: 10.1016/j.clim.2017.04.001]
12. Ahs C, Dothard EH, Garner ML, Feldman SR, Huang WW. To test or not to test? An updated evidence-based assessment of the value of screening and monitoring tests when using systemic biologic agents to treat psoriasis and psoriatic arthritis. JAMA Dermatol 2015; 73: 420-428.e1 [PMID: 26184440 DOI: 10.1001/j.amadermatol.2015.06.004]
13. Craxì A, Perno CF, Viganò M, Cicerchini-Silberstein F, Petta S, AdHoc (Advancing Hepatitis C for the Optimization of Cure) Working Party. From current status to optimization of HCV treatment: Recommendations from an expert panel. Dig Liver Dis 2016; 48: 995-1005 [PMID: 27388261 DOI: 10.1016/j.dld.2016.06.004]
14. World Health Organization. Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection; updated version April 2016. Available from: URL: http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1
15. Mistry N, Shapero J, Crawford RJ. A review of adverse cutaneous drug reactions resulting from the use of interferon and ribavirin. Can J Gastroenterol 2009; 23: 677-683 [PMID: 19826642 DOI: 10.1155/2009/651952]
16. González-Grande R, Jiménez-Pérez M, González Arjona C, Mostazo Torres J. New approaches in the treatment of hepatitis C. J World Gastroenterol 2016; 22: 1421-1432 [PMID: 26819511 DOI: 10.3748/vw.v22.i14.1421]
17. García-Lora E, Tercedor J, Massare E, López-Nevet MA, Skilo M, García-Mellado V. Interferon-induced psoriasis in a patient with chronic hepatitis C. Dermatology 1993; 187: 280 [PMID: 8274788 DOI: 10.1159/000024766]
18. Pauluzzi P, Kokelj F, Perkan V, Pozzato G, Moretti M. Psoriasis exacerbation induced by interferon-alpha. Report of two cases. Acta Derm Venereol 1993; 73: 395 [PMID: 7904414]
19. Erkèk E, Karaduman A, Akcan Y, Sökmenşıer C, Bükülmez G. Psoriasis associated with HCV and exacerbated by interferon-alpha: complete clearance with acitretin during interferon alpha treatment for chronic active hepatitis. Dermatology 2000; 201: 179-181 [PMID: 11053930 DOI: 10.1159/000018447]
20. Downs AM, Dunill MG. Exacerbation of psoriasis by interferon-alpha therapy for hepatitis C. Clin Exp Dermatol 2000; 25: 351-352 [PMID: 10971502 DOI: 10.1046/j.1365-2230.2000.00655.x]
21. Afshar M, Martinez AD, Gallo RL, Hata TR. Induction and exacerbation of psoriasis with Interferon-alpha therapy for hepatitis C: A review and analysis of 36 cases. J Eur Acad Dermatol Venereol 2013; 27: 771-778 [PMID: 22671985 DOI: 10.1111/j.ejdv.12083.04582.x]
22. Ahmad QM, Sameen F, Shah IH. Prevalence of hepatotropic viruses b&c in psoriasis - A study from kashmir. Indian J Dermatol 2005; 50: 200-202 Available from: URL: http://www.e-ijd.org/text.asp?2005/50/4/200/19744
23. Johnson-Huang LM, Suárez-Fariñas M, Pierson KC, Fuentes-Duculan J, Cueto I, Lentini T, Sullivan-Whalen M, Gilleaudeau P, Krueger JG, Haider AS, Lowe MA. A single intradermal injection of INF-γ induces an inflammatory state in both non-lesional psoriatic and healthy skin. J Invest Dermatol 2012; 132: 1177-1187 [PMID: 22277938 DOI: 10.1038/jid.2011.458]
24 Imafuku S, Naito R, Nakayama J. Possible association of hepatitis C virus infection with late-onset psoriasis: a hospital-based observational study. *J Dermatol* 2013; 40: 813-818 [DOI: 10.1111/1346-8138.12240]

25 Taha EA, Mekky MA, Morsy H, Saleh MA, Nafeh HM, Ez-Aldin AM, Sayed SK. Study of the impact of viral load of hepatitis C on patients with concomitant psoriasis vulgaris. *Arab J Gastroenterol* 2014; 15: 98-102 [PMID: 25174792 DOI: 10.1016/j.ajg.2014.08.001]

26 Piaserico S, Dapavo P, Conti A, Gisondi P, Russo FP. Adalimumab is a safe option for psoriasis patients with concomitant hepatitis B or C infection: a multicentre cohort study of 37 patients and review of the literature. *J Eur Acad Dermatol Venereol* 2017; 31: 1853-1859 [PMID: 28146345 DOI: 10.1111/jdv.14146]

27 Navarro R, Villarasa E, Herranz P, Puig L, Bordes X, Carrascosa JM, Taberner R, Ferrán M, García-Bustinduy M, Romero-Maté A, Pedragosa R, García-Diez A, Daudén E. Safety and effectiveness of ustekinumab and antitumour necrosis factor therapy in patients with psoriasis and chronic viral hepatitis B or C: a retrospective, multicentre study in a clinical setting. *Br J Dermatol* 2013; 168: 609-616 [PMID: 22985451 DOI: 10.1111/bjd.12045]

28 Costa L, Caso F, Atteno M, Giannitti C, Spadaro A, Ramonda R, Vezzù M, Del Puente A, Morisco F, Fiocco U, Galeazzi M, Punzi L, Scarpa R. Long-term safety of anti-TNF-α in PsA patients with concomitant HCV infection: a retrospective observational multicenter study on 15 patients. *Clin Rheumatol* 2014; 33: 273-276 [PMID: 23975363 DOI: 10.1007/s10067-013-2378-0]

29 Salvi M, Macaluso L, Luci C, Matteozi C, Paolino G, Aprea Y, Calvieri S, Richetta AG. Safety and efficacy of anti-tumor necrosis factor α in patients with psoriasis and chronic hepatitis C. *World J Clin Cases* 2016; 4: 49-55 [PMID: 26881191 DOI: 10.12998/wjcc.v4.i2.49]

30 Morisco F, Guarino M, La Bella S, Di Costanzo L, Caporaso N, Ayala F, Balato N. Lack of evidence of viral reactivation in HBsAg-negative HBeAb-positive and HCV patients undergoing immunosuppressive therapy for psoriasis. *BMC Gastroenterol* 2014; 14: 214 [PMID: 25523080 DOI: 10.1186/s12876-014-0214-x]

31 Burchill MA, Golden-Mason L, Wind-Rotolo M, Rosen HR. Memory re-differentiation and reduced lymphocyte activation in chronic HCV-infected patients receiving direct-acting antivirals. *J Viral Hepat* 2015; 22: 983-991 [PMID: 26482547 DOI: 10.1111/jvh.12465]

32 Spaan M, van Oord G, Kreeft K, Hou J, Hansen BE, Janssen HL, de Knegt RJ, Boonstra A. Immunological Analysis During Interferon-Free Therapy for Chronic Hepatitis C Virus Infection Reveals Modulation of the Natural Killer Cell Compartiment. *J Infect Dis* 2016; 213: 216-223 [PMID: 26223768 DOI: 10.1093/infdis/jiv391]

33 Serti E, Park H, Keane M, O’Keefe AC, Rivera E, Liang T, Ghany M, Rehermann B. Rapid decrease in hepatitis C viremia by direct acting antivirals improves the natural killer cell response to IFNα. *Gut* 2017; 66: 724-735 [PMID: 26733671 DOI: 10.1136/gutjnl-2015-310033]

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