

Psoriasis as a Manifestation of an Immune Reconstitution in Two Patients with Hepatitis C Treated with Ledipasvir/Sofosbuvir

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Psoriasis is a common inflammatory disease of the skin, affecting approximately 2% of the world's population (1). Induction and exacerbation of skin lesions can be triggered by various exogenous factors, including drugs. Agents that are frequently reported, yet controversial, are beta-blockers, anti-malarials, lithium, imiquimod, angiotensin-converting enzyme, non-steroidal anti-inflammatory drugs (NSAIDs) and interferon (IFN)- α (2).

We describe here the first 2 cases of occurrence of plaque-type psoriasis in 2 patients with hepatitis C treated with ledipasvir/sofosbuvir (Harvoni[®]).

CASE REPORTS

Case 1. A 65-year-old man with classic chronic plaque-type psoriasis for more than 30 years was infected by the hepatitis C virus (HCV), genotype 1a, in January 2001 by an unknown route of transmission. First-line combined treatment with pegylated interferon (IFN)- α and ribavirin (from June to August 2001) was stopped due to exacerbation of his psoriatic skin lesions. After a period of 14 years with no antiviral treatment and the presence of few persistent psoriatic plaques on his elbows, hepatitis C virus RNA serum levels increased up to 6.900.000 IU/ml. Therefore, the patient had been treated with ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni[®]) orally once daily since late January 2015. While HCV RNA serum level decreased rapidly and continuously to 20 IU/ml, approximately 2 months after the beginning of the antiviral treatment a massive exacerbation of psoriasis, with a Psoriasis Area and Severity Index (PASI (3)) score of 37.5, occurred (Fig. 1). None of the exogenous triggers listed above was relevant, especially no other chronic infections, such as acquired immunodeficiency syndrome or hepatitis B. By using topical emollients, corticosteroid ointments and dithranol combined with narrow-band ultraviolet B (UVB 311nm) phototherapy the psoriatic skin lesions improved rapidly within 7 weeks without withdrawal of the antiviral treatment (PASI score after treatment 9.5).

Case 2. A 43-year-old man had had chronic hepatitis C, virus genotype 1b, since 2008 by unknown route of transmission. First-line combined treatment with pegylated IFN- α and ribavirin was given in 2009, with only a partial response, but with no skin reactions. Since hepatitis C virus RNA serum levels remained distinc-

tly elevated (1.860.000 IU/ml) he received ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni[®]; Gilead Sciences International Ltd., Cambridge, UK) orally once daily from July until October 2015. Three months after initiating therapy hepatitis C viral load was below the limit of detection, which was considered as complete response. However, at the same time patient developed classic plaque-type psoriasis in the absence of any other exogenous triggers. Furthermore, there was no previous medical or family history of psoriasis. On consultation in our department in March 2016, lesions at typical locations, such as the elbows and knees, could be seen (PASI score 7.4), which were treated successfully with corticosteroid and calcipotriol ointments.

DISCUSSION

Whereas an epidemiological association between psoriasis vulgaris and hepatitis C virus infection has been reported in the past (4, 5), data about the pathogenetic interaction of both conditions are very limited. It is suggested that hepatitis C virus infection itself especially may trigger late-onset psoriasis vulgaris via tumour necrosis factor (TNF)- α , which acts as a common mediator in both diseases (4).

Regarding all antiviral treatment options including protease- and non-structural protein 5A/B (NS5A/B)-



Fig. 1. Clinical findings for Case 1 showing a massive exacerbation of the pre-existing plaque psoriasis. Extensively confluent erythematous plaques are remarkable.

inhibitors) available for patients with hepatitis C until recently, an induction or exacerbation of psoriasis has so far only been observed subsequent to treatment with pegylated or non-pegylated IFN- α , either as monotherapy or combined with ribavirin (6). In detail, several observations indicate a direct relationship between IFN- α and the development of psoriatic lesions, as the cytokine is transiently produced by plasmacytoid pre-dendritic cells at very early stages of plaque development (7).

In October 2014, the US Food and Drug Administration (FDA) approved the fixed combination of the 2 direct-acting antiviral drugs, ledipasvir/sofosbuvir (Harvoni[®]), for the treatment of HCV genotype 1 infections (8). Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which acts as a chain terminator, whereas ledipasvir is an NS5A inhibitor. Its exact mechanism of action is unknown, but a suggestion is an inhibition of hyperphosphorylation of NS5A, which seems to be required for viral production (8). The most common side-effects of Harvoni[®] seen in recent trials were fatigue, headache, insomnia, and nausea (9). A skin rash, with no further characterization, is reported in up to 7% of treated patients (9). However, an induction of novel or exacerbation of pre-existing psoriasis has, to the best of our knowledge, not yet been reported.

In both cases criteria for likelihood of a causal relationship between drug exposure and the reported adverse events, according to the World Health Organization (WHO) Uppsala Monitoring centre guidance for classifying drug reactions (10), are not completely fulfilled:

Regarding case 1, withdrawal of the suspected drug and following re-exposure was not possible. As initial hepatitis C virus RNA serum levels were high, the drug was considered essential in the treatment of the patient's hepatitis C infection and withdrawal of Harvoni[®] was ethically not justifiable.

Regarding case 2, first manifestation of plaque-type psoriasis occurred 3 months after treatment initiation with ledipasvir/sofosbuvir. Therefore, close temporal link between therapy and potential side-effect is not given.

With regard to the timely relation of psoriasis and ledipasvir/sofosbuvir treatment in the observed cases, immune reconstitution upon successful treatment and significant decrease of virus load may be a possible explanation. In the medical literature, a similar phenomenon, the so called "immune reconstitution inflammatory syndrome" (IRIS), is reported in the context of progressive multifocal leukoencephalopathy (PML) in patients with HIV (11), as well as in patients with multiple sclerosis treated by natalizumab (12).

In patients with chronic hepatitis C, increased levels of FoxP3-positive regulatory T cells are found (13, 14). Thus, it may alternatively be hypothesized according

to the concept of T-cell plasticity (15), that a successful therapy of the hepatitis C infection as recognizable by normalizing hepatitis C virus RNA serum levels leads to a transformation of FoxP3-positive regulatory T cells (Tregs) into IL-17-producing T cells, which in turn causes the exacerbation of the psoriatic lesions.

With this in mind, these cases highlight a possible novel unwanted effect of ledipasvir/sofosbuvir (Harvoni[®]). Further observations and histopathological explorations in large treatment cohorts may be necessary to define the incidence and the exact pathomechanism for this specific exacerbation of psoriasis.

The authors declare no conflicts of interest.

REFERENCES

1. Lebowitz M. Psoriasis. *Lancet* 2003; 361: 1197–1204.
2. Armstrong AW. Psoriasis provoked or exacerbated by medications: identifying culprit drugs. *JAMA Dermatol* 2014; 150: 963.
3. Fredriksson T, Petterson U. Severe psoriasis-oral therapy with a new retinoid. *Dermatologica* 1978; 157: 238–244.
4. 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.
5. Taha EA, Mekky MA, Morsy H, Saleh MA, Nafeh HM, Ez-Aldin AM, et al. Study of the impact of viral load of hepatitis C on patients with concomitant psoriasis vulgaris. *Arab J Gastroenterol* 2014; 15: 98–102.
6. 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.
7. Nestle FO, Conrad C, Tun-Kyi A, Homey B, Gombert M, Boyman O, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. *J Exp Med* 2005; 202: 135–143.
8. Gritsenko D, Hughes G. Ledipasvir/Sofosbuvir (Harvoni): improving options for hepatitis c virus infection. *Pharm Therapeut* 2015; 40: 256–276.
9. Afdhal M, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; 370: 1889–1898.
10. Safety monitoring of medicinal products. Guidelines for setting up and running a Pharmacovigilance Centre [accessed February 16, 2016]. Available from: <http://www.who-umc.org/graphics/24747.pdf>.
11. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology* 2009; 72: 1458–1464.
12. Tan IL, McArthur JC, Clifford DB, Major EO, Nath A. Immune reconstitution inflammatory syndrome in natalizumab-associated PML. *Neurology* 2011; 77: 1061–1067.
13. Manigold T, Shin EC, Mizukoshi E, Mihalik K, Murthy KK, Rice CM, et al. Foxp3+CD4+CD25+ T cells control virus-specific memory T cells in chimpanzees that recovered from hepatitis C. *Blood* 2006; 107: 4424–4432.
14. Zhai N, Chi X, Li T, Song H, Li H, Jin X, et al. Hepatitis C virus core protein triggers expansion and activation of CD4(+)CD25(+) regulatory T cells in chronic hepatitis C patients. *Cell Mol Immunol* 2015; 12: 743–749.
15. Gatzka M, Scharffetter-Kochanek K. T-cell plasticity in inflammatory skin diseases – the good, the bad, and the chameleons. *J Dtsch Dermatol Ges* 2015; 13: 647–652.