Skin Adverse Events During Dual and Triple Therapy for HCV-Related Cirrhosis

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1. Introduction

Adverse cutaneous reactions are described in standard of care (SOC) therapy with peginterferon-alpha (PEG-IFN) and ribavirin (RBV) (1). These tend towards a uniform entity of dermatitis, characterized by generalized pruritus and skin xerosis, with eczematiform lesions accentuated by erythematous papules and microvesicles that are often excoriated, predominantly located on the extremities and on truncal skin sites exposed to friction. Management of these eruptions can be achieved with the same approach as for eczema (topical corticosteroids and emollients), usually without the need for discontinuation of the antiviral treatment (2).

Two protease inhibitors, boceprevir and telaprevir, recently approved for the treatment of genotype 1 HCV infection in combination with PEG-IFN and RBV have been associated with a higher sustained virological response rate than SOC therapy. During triple therapy an increased incidence of skin adverse events is described: in triple therapy phase II and III trials it has been reported a 55% rate of cutaneous adverse events compared with 33% in the PEG-IFN and RBV controls. Skin lesions during dual and telaprevir-containing triple therapy are similar, but the severity and frequency are significantly higher in triple therapy compared with dual therapy.

We report the case of a 64 year old man with HCV genotype 1 who discontinued telaprevir therapy because of severe skin eruptions and who, during ribavirin and interferon treatment, after a period free of skin lesions, developed new dermatological lesions different than those experienced during telaprevir treatment.

Conclusions: Several adverse effects are associated to anti-HCV drugs, hence appropriate skin care management and follow-up are very important. A careful anamnesis before the initiation of triple therapy is necessary to identify previous dermatological diseases that could increase skin adverse effects incidence.

Keywords: Liver Cirrhosis; Telaprevir; Skin Diseases

Implication for health policy/practice/research/medical education: A careful anamnesis before the initiation of triple therapy is necessary to identify previous dermatological diseases that could increase skin adverse effects incidence. Other studies are necessary to evaluate the real risk of cutaneous manifestations in HCV treatment, through the findings of clinical, hematological or genetic factors.

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HCV-RNA became detectable, so PEG-IFN and RBV therapy was discontinued. The patient has never experienced any recurrence of dermatological lesions.

3. Conclusions

HCV is the major cause of chronic liver disease that gradually progresses from chronic hepatitis to cirrhosis and hepatocellular carcinoma (HCC) during the course of infection. Dermatological adverse events are described during HCV therapy. The traditional treatment PEG-IFN plus RBV combination therapy is associated with inflammatory skin lesions at the site of injection. The type of skin reactions observed are vesicle-like erythematous eruptions at the injection sites, and pruritic papular erythematous eruptions located on the face, neck, distal limbs, dorsa of-like erythematous eruptions away from the injection sites and autotrsenilitization dermatitis apart from injection sites have not been reported frequently (5). Manjon-Haces et al described a series of 210 patients in Spain under HCV treatment with interferon alfa-2b plus ribavirin. Fourteen patients experienced localized while two had generalized eczematous lesions (6).

At twenty-four weeks of treatment erythematous lesions localized on the inner part of both thighs appeared, soon after the injection of interferon. These lesions resolved spontaneously, without any treatment. At the same time, HCV-RNA became detectable, so PEG-IFN and RBV therapy was discontinued. The patient has never experienced any recurrence of dermatological lesions.
Dereure et al. (7) described the most extensive series with diffuse inflammatory lesions. They observed 20 patients that presented eczema-like skin lesions mainly on the extremities and sometimes associated with photosensitivity. The clinical pattern was a pruritic, confluent, papular erythematous eruption admixed with occasional vesicles. Lesions were predominantly located on the distal limbs, dorsum of the hands, face, neck and, less frequently, the trunk, axillae and buttocks. Other cutaneous side-effects at a distance from injection points include the occurrence or worsening of psoriasis, lichen planus, vitiligo, alopecia areata, lupus erythematosus, sarcoidosis, aphthae, Meyerson’s phenomenon and nummular dermatitis (8).

The introduction of the new triple-therapy including telaprevir has brought an improvement of SVR but led to an increased incidence of skin side effects in respect to SOC. More than 90% of reports were either mild (37% grade 1) or moderate (14% grade 2) skin adverse events and > 90% of cases were stable, remaining unchanged until the end of telaprevir treatment with no progression to a more severe grade. The most common presentations are characterized by pruritus, xerosis, erythematous papules, vesicles and excoriated lesions located on the trunk, extremities and friction sites (9). The pattern of lesions are similar to rash associated with PEG-IFN and RBV therapy alone but greater in frequency (55% vs 33%) and severity (3.7% vs 0.4%) (9).

A small proportion of patients (6%) experienced more severe skin conditions. However, a few patients presented with SCAR manifestations: three cases of SJS and 11 cases of DRESS were suspected, with 2 SJS and 3 DRESS cases, but these also resolved after treatment discontinuation (9). In our case, patient was naïve to HCV treatment and he denied previous history of inflammatory skin disease. During triple-therapy including telaprevir, he showed compatible cutaneous ADR which led to stopping of protease inhibitor and continuing PEG-IFN and RBV treatment. At twenty-four weeks also SOC was discontinued because HCV-RNA was detectable again. To date, the pathogenic mechanisms of telaprevir-related skin lesions are still unknown.

This case leaves a number of questions open: are the dermatological lesions appeared on the fifth only due to telaprevir or are they the consequence of PEG-IFN and RBV too? Can telaprevir administration unmask pathogenetic mechanisms that would explain cutaneous effects to PEG-IFN and RBV when stopping telaprevir? The patient would have had effects on the skin to ribavirin even if he had not been previously treated with telaprevir?

In conclusion, several adverse effects are associated to anti-HCV drugs, hence appropriate skin care management and follow-up are very important. A careful anamnesis before the initiation of triple therapy is necessary to identify previous dermatological diseases that could increase skin adverse effects incidence. Other studies are necessary to evaluate the real risk of cutaneous manifestations in HCV treatment, through the findings of clinical, hematological or genetic factors.

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Authors have nothing to declare.

Authors’ Contribution
Study concept and design: Alessandro Federico, Dolores Sgambato, Gaetano Cotticelli, Antonietta Gerarda Gravina, Filippo Beneduce. Acquisition of data: Alessandro Federico, Marcello Dallio, Eleonora Ruocco, Filippo Beneduce. Analysis and interpretation of data: Alessandro Federico, Marco Romano, Carmela Loguercio. Drafting of the manuscript: Alessandro Federico, Dolores Sgambato, Gaetano Cotticelli. Critical revision of the manuscript for important intellectual content: Alessandro Federico, Marco Romano, Carmela Loguercio. Study supervision: Carmela Loguercio.

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