

Severe form of psoriasis occurring

after peginterferon plus ribavirin treatment, and frequent resort to filgrastim rescue, in a woman treated for a chronic HCV infection

Short title: Diffuse psoriasis during peginterferon-ribavirin-filgrastim treatment of HCV infection

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Abstract

Associated treatment with pegylated interferon plus specific antiviral compounds significantly improved the prognosis of chronic hepatitis C and B, although antiviral drugs (especially interferon and its derivatives) tend to be myelotoxic and also some rescue treatments, like human recombinant granulocyte colony-stimulating factors (which are extensively administered in order to correct neutropenia induced by antiviral therapy), may also be involved in prompting or exacerbating cutaneous psoriasis and its systemic complications. A representative case report of a woman with a chronic, progressive, hepatitis C, who underwent long-term treatment with combined pegylated interferon plus ribavirin, and resorted to multiple cycles of filgrastim to recover a severe, recurring granulocytopenia caused by antiviral therapy itself, and to maintain an effective dosage of anti-HCV antivirals, developed an extensive and severe cutaneous psoriasis, which improved only after specific cyclosporin treatment. From a pathogenetic point of view, in our case it remains extremely difficult to distinguish the role of pegylated interferon from that of the accompanying ribavirin, from that of the frequently administered granulocyte growth factor (filgrastim), since all mentioned drugs were administered concurrently during many months, and according to the existing literature evidences, all of them have a potential to induce psoriasis as a potential untoward effect in subjects suffering from chronic hepatitis. Cyclosporin treatment obtained a stable remission of this last severe cutaneous complication, but the efforts to contain the progression of the underlying evolutive hepatitis C were blunted by the difficult-to-treat genotype 1 HCV infection, and the frequent need to lower drug dosages and/or to interrupt antiviral therapy, because of myelotoxic and later cutaneous complications prompted by anti-HCV therapy itself.

Key words: adverse event, chronic HCV infection, filgrastim, neutropenia, pegylated interferon, psoriasis, ribavirin

Introduction

As known since many years, chronic hepatitis C is often a progressive disease, leading to serious hepatic damage (including liver cirrhosis and decompensation, hepatocarcinoma, and multiform HCV-related immune-mediated abnormalities). The novel formulations of interferons (pegylated interferons) plus the administration of a specific antiviral for this RNA virus (ribavirin), significantly changed the natural history of chronic HCV infection, leading to elevated rates of complete cure, or at least to a reduced and slower rate of disease progression towards end-stage liver disease, as well as a to reduced frequency of frank liver cirrhosis and neoplastic complications^{1,2}. However, although increasing the proportion of patients with sustained virological and clinical response, pegylated interferons and established ribavirin dosages remarkably contribute to raise more frequent and intense adverse effects^{1,3}. In a special population like that composed by patients co-infected by HIV, the main predictors of hematological toxicity following pegylated interferon-ribavirin therapy for HCV treatment seemed to be represented by concurrent zidovudine administration, an underlying cirrhosis, a low body weight, and baseline hemoglobin levels <14 g/dL⁴, but these data need confirmation by larger experiences involving hepatitis-monoinfected individuals.

In fact, both compounds largely employed in the management of chronic HCV hepatitis (until now, the different interferon formulations, and ribavirin), are burdened by a broad range of untoward effects^{3,5}, although myelotoxicity represents the most frequent cause of drug dosage reduction and/or resort to combined treatments aimed at maintaining a sufficient leukocyte, erythrocyte, and platelet count, to avoid interruption of antiviral therapy or prolonged lowering of drug dosages, which may seriously affect the final outcome of antiviral management of chronic hepatitis C. In fact, since 2005 consensus guidelines were developed on how to manage the most fre-

quent hematologic complications of hepatitis C treatment⁶: a more prompt and “aggressive” use of specific growth factors (i.e. erythropoietin for anemia, and granulocyte colony-stimulating factors for neutropenia), as well as antidepressants and anxiolytics for some central nervous system disturbances³, together with continued antiviral therapy possibly maintained at adequate dose regimens, was strongly recommended since several years^{3,7,8}, in order to maximize adherence, prevent dose reductions, improve the quality of life, and increase the number of subjects completing the established cycle of peginterferon-ribavirin therapy at the most effective dosages. A number of implications, including regulatory and pharmacoeconomic ones, are of relevant importance, since no randomized studies are available until now, and especially the use of growth factors in patients without a far advanced hepatic disease (i.e. frank liver cirrhosis), continue to receive these costly support medications, mostly delivered on an “off-label” basis^{3,9}.

Notwithstanding the potent activity of present therapeutic associations against HCV infection, selected patients (such as those with multiple liver co-infections, those co-infected by HIV, and those infected by selected HCV genotypes like HCV genotype 1), are at increased risk of a reduced response rate, and a greater frequency of relapses after treatment, so that re-treatment with existing drugs, or waiting for further therapeutic resources², are the present solutions for non-responders or relapsers. Finally, an optimized physician-patient relationship may add significantly to such a demanding treatment like that for chronic hepatitis, and it is expected to play a crucial role in overcoming the majority of psychosomatic untoward events and the need of frequent clinical-laboratory controls, as well as the frequent administration of oral and parenteral drugs, including those implicated in the correction and control of adverse events stemming from antiviral protocols themselves^{9,10}.

Case report

A 54-year-old female patient who received in the past multiple blood transfusions, had a diagnosis of chronic HCV infection since the age of 47, after an occasional retrieval of persistently altered serum transaminases, and a first positive anti-HCV serology. Two years later, the combination of a liver biopsy examination which showed a histopathologic picture of aggressive chronic hepatitis, and elevated plasma HCV-RNA levels, prompted a first therapeutic course with associated interferon-alpha and ribavirin, interrupted after four months, predominantly due to severe, relapsing leukopenia. One year later, despite proportionally low serum cytotoxic levels (GOT 42, GPT 45 U/L), an elevated quantitative HCV-RNA was detected again ($1,620 \times 10^3$ copies/mL, branched-DNA technique), but genotypic testing revealed an unfavorable 1b HCV genotype, so that our patient refrained from a novel treatment, and preferred a periodical clinical-laboratory-ultrasonographic monitoring. Twenty months later, the availability of pegylated interferons allowed us to try a novel anti-HCV course performed with pegylated interferon-alpha 2a (at 180 mcg/week s.c.), plus ribavirin (at 800 mg/day orally). Despite multiple, repeated episodes of relevant neutropenia and thrombocytopenia, already occurring during the first month of treatment (with a nadir of the absolute neutrophil count repeatedly <750 cells/ μ L), which accompanied our patient during the entire anti-HCV treatment course and led to frequent drug dosage adjustments and especially to repeated 2-5-day cycles of s.c. filgrastim (rHuG-CSF) to recover granulocytopenia, a virological success was obtained, as expressed by HCV-RNA undetectability reached after three months and maintained thereafter, and serum liver enzymes reaching and maintaining normal limits, although after the sixth month the peginterferon dosage was reduced to 135 mcg/week, and the ribavirin dose was steadily reduced to 600 mg/day, due to persisting myelotoxicity. Notwithstanding the above-mentioned drug dosage reduction, further, multiple filgrastim cycles of 2-3-day duration became often necessary to correct neutropenia (i.e. absolute neutrophil levels <750 cells/ μ L). Although the 12-month course of peginterferon-ribavirin was completed successfully, only three months later our patient experienced a breakthrough of both HCV replication ($2,475 \times 10^3$ copies/mL), associated with newly elevated serum liver enzymes (GOT 70, GPT 86 U/L), while blood cell count tested within normal limits. Our “relapser” patient continued her periodic clinical-laboratory monitoring, which 15 months after the end of the previous treatment course disclosed a persistently elevated HCV replication (plasma HCV-RNA $1,950 \times 10^3$ copies/mL), and permanently altered cytotoxic indexes (GOT 63, GPT 63 U/L). Seven months later, a novel histopathologic examination was performed through liver biopsy: a progressive, moderate to severe liver cirrhosis was found (with an overall Knodell score of 11), which was judged as frankly worsened in comparison with the previous liver histopathological examination obtained nearly four years before. Because of this unfavorable disease course, and despite the presence of a genotype 1 HCV disease which fa-

Aim of our present report is to describe an infrequent case of appearance of a severe, extensive form of psoriasis in a woman mono-infected with HCV, who developed for the first time this relevant complication during concurrent treatment with pegylated interferon, ribavirin, and her frequent resort to granulocyte colony-stimulating factor to recover neutropenia and maintain effective antiviral dosages, after failures of prior anti-HCV therapeutic attempts, and a concurrent evolution of her chronic hepatitis towards a liver cirrhosis. Our case report is discussed on the ground of the available literature evidences, which report infrequent cases of psoriasis which occurred or were re-exacerbated among patient affected by chronic viral hepatitis (either HCV or HBV hepatitis), and received specific antivirals with or without recombinant granulocyte growth factors, although in our case the concurrent administration of two anti-HCV antivirals (peginterferon plus ribavirin), and the prolonged, repeated resort to filgrastim to recover neutropenia, does not allow us to target the specific responsibility of one single drug versus the remaining others.

vored a relapse after 12 months of an apparently satisfactory treatment, another therapeutic attempt with the same drugs (pegylated interferon alpha-2a at 180 mcg/week, plus ribavirin at 1,000 mg/day), was carried out seven months later. Once again, both thrombocytopenia (never associated with bleeding), and especially granulocytopenia complicated the treatment course since the first weeks of therapy, so that s.c. filgrastim cycles were repeated with increased frequency (starting from filgrastim 300 mcg 2-3 days every two weeks during the first three months, up to filgrastim 300 mcg twice weekly, delivered from the fourth month of anti-HCV therapy, in order to maintain as far as possible the full dosage of both peginterferon and ribavirin, which in the meantime allowed and sustained some amelioration of both HCV-RNA levels (until 675-956 copies/mL), and serum transaminases (until GOT 56-61, and GPT 43-76 U/L), although virus undetectability and normal liver enzymes were never detected during this last therapeutic course. At the start of the fifth month of combined peginterferon-ribavirin treatment frequently supported by s.c. filgrastim, numerous, itching and desquamation, plaque lesions first appeared on the scalp hair, and were treated with local betamethasone, with limited benefit. Entering the sixth month of combined anti-HCV treatment, and still in absence of a complete virological and liver enzyme response, an overwhelming worsening of the cutaneous lesions and plaques appeared in a scattered form involving the 75% of body, so that numerous dermatological consultations were recommended, and skin biopsies confirmed a diagnosis of frank psoriasis. One month later, despite the interruption of anti-HCV therapy at its seventh month, s.c. filgrastim was still needed (at 3000 mcg, three times weekly), in order to prepare our patient to a systemic cyclosporine treatment, since granulocytopenia tended to persist despite peginterferon-ribavirin interruption (the absolute neutrophil count still tested <750 cells/ μ L). Waiting for cyclosporine administration, and during filgrastim rescue therapy a significant worsening of the psoriasis picture occurred, and also a temporary, systemic steroid treatment performed for two weeks, achieved only a limited and very transient benefit (acting better on the itching symptoms), while a significant worsening of the diffuse skin psoriasis (involving extensively face and head, trunk, elbows and limbs, for an overall 75% of the patient's body), occurred after steroid suspension, until systemic cyclosporin was finally delivered at full dosage (400 mg/day, later reduced to 250 mg/day, six days a week). This last cyclosporine treatment obtained for the first time a partial remission of the systemic psoriasis, which after a three-month follow-up was still characterized by a severe, systemic cutaneous involvement, in absence of further complications. In the meantime, unfortunately the underlying chronic HCV disease did not stop its unfavorable evolution towards a frank liver cirrhosis.

Discussion

During the past two decades, interferons became widely prescribed for systemic therapy of chronic hepatitis, malignancies, and other pathologic conditions. Well-known cutaneous side effects of interferons and their derivatives are represented by dry skin, pruritus, and especially temporary hair loss.

The first, anecdotal literature reports of a possibly induced or worsened psoriasis come to our attention in early-mid nineties (1993-1997)¹¹⁻¹⁹, when just non-pegylated interferon-alpha was the most used compound compared with other interferons, widely administered especially for the treatment of both chronic hepatitis B and hepatitis C, thus confirming that the underlying type of liver infection (hepatitis B or C)¹¹⁻¹⁹, does not seem to play a role in prompting or exacerbating this untoward complication, and the role of interferon itself was largely preponderant compared with that of ribavirin (which was extensively used in HCV-infected patients, during subsequent years: in fact, as far as we know no reports of psoriasis apparently induced by ribavirin alone are retrievable). During mid-nineties, some authors claimed an autoimmune reaction as the potential supporting pathogenesis of these events in subjects with a chronic hepatitis treated with interferon preparations¹⁴, while some forms of psoriasis complicated by arthritis (psoriasis arthropathy), were attributed to a direct association between interferon-alpha therapy and the development of a seronegative arthritis¹⁵⁻¹⁸, and in a particular case a seronegative and a HLA-antigen-negative oligoarthritis-sacroiliitis was also complicated by a spinal involvement¹⁸. During subsequent years (2000-2007) some other reports came from the international literature²⁰⁻²⁶; all of them involved patients treated for chronic hepatitis C with both (peg)interferon plus ribavirin, with a different described outcome upon treatment interruption and rechallenge (i.e. resolution or not of psoriasis after discontinuation of anti-HCV therapy, and more frequent re-exacerbation upon eventual rechallenge with the same drugs). Some authors of this last reports recognized a similar potential for the pegylated derivatives of interferon, too, co-administered with ribavirin^{22,24-26}, and in the majority of episodes psoriasis ameliorated or disappeared after anti-HCV treatment interruption, although the outcome of chronic viral hepatitis was often unfavorable save in one case²⁵, mostly due to the early appearance of psoriatic skin lesions, and the need to stop interferon-ribavirin treatment well before the completion of therapeutic course. From a pathogenetic point of view, differently from other authors who advocated some immune-mediated mechanisms (even when a pyoderma gangrenosum occurred together with a psoriasis exacerbation)²⁶, Yamamoto and coworkers already in 1995 raised the hypothesis that HCV infection itself still not treated with antivirals, might trigger the appearance and/or the exacerbation of psoriasis via some hypothesized HCV-immune-mediated pathogenetic mechanisms²⁷, thus diminishing the potential role of interferon and other antivirals in prompting psoriasis in hepatitis C patients, while on the other hand in the same year and in the same Journal, Rahamimov et al. claimed that psori-

riasis should not be considered a contraindication for interferon therapy during chronic hepatitis C²⁸, thus contributing to make even less clear the epidemiological, pathogenetic, and clinical links among these occurrences in clinical practice, and making strongly needed further investigations in this field, which retains relevant scientific and clinical-practical, unanswered features. On the other hand, another 2005 single case report underlined the role of pegylated interferon alpha-2b in inducing a novel-onset extensive psoriasis after the first four weeks of treatment of a chronic hepatitis B (not due to HCV), which disappeared after treatment interruption²⁹, so that the role of (peg) interferon itself seemed to overcome that of chronic hepatitis in conditioning this serious skin complication. One year before, a 10-year-old girl who received interferon alpha-2a for a chronic hepatitis B too, experienced the concurrent appearance of psoriasis and vitiligo, which remained even after stopping interferon therapy³⁰.

To further complicate these cumbersome etiologic and pathogenetic issues, the role of granulocyte growth factors, and in particular that of the mostly used recombinant human growth factor in this field (i.e., rHuG-CSF), deserve major attention. In fact, although two literature reports described anecdotal cancer patients who suffered from extensive, complicated psoriasis or an exacerbation of palmoplantar pustulosis after filgrastim and lenograstim (rHuG-CSF) treatment^{31,32}, there is a contrasting evidence published by Hino et al., who observed a favorable activity of filgrastim on a long-lasting case of pustulosis palmaris and plantaris, probably attributable to the concurrently increased leukocyte/neutrophil count³³. Coming to patients with an underlying chronic hepatitis, the apparent worsening of clinical picture of psoriasis in our patient chronically infected with HCV and concurrently treated with peginterferon-ribavirin remains of very difficult pathogenetic interpretation, on our opinion.

4

Our infrequent case report raises some intriguing and still unanswered questions in this field: the role of (peg)interferon and that of ribavirin in the appearance or exacerbation of psoriasis, the role of underlying hepatitis C, hepatitis B, or other potential indications for (peg) interferon treatment in developing or exacerbating psoriasis, the time of onset and the intensity, duration, and tendency to resolve of this cutaneous-systemic complication upon anti-hepatitis treatment withdrawal, the weighted amelioration or cure of chronic liver disease compared with the exacerbation of mild-to-moderate cutaneous psoriasis lesions, the eventual role played by the adjunct of a recombinant human growth factor (i.e. filgrastim) in the pathogenetic and clinical disease course, and the overall dermatologic and hepatologic management of these special patients. On the ground of the existing literature, which is presently founded on anecdotal, retrospective, often single case reports, further, in-depth studies appear strongly needed to clarify the frequency, the clinical features, the duration and the outcome of psoriasis, with particular regard focused on the consequences on the concurrent treatment of chronic

liver disorders. Major pathogenetic advances are expected to greatly help both prevention and management of these invalidating complications, which are expected to become more and more frequent in the meantime, paralleling the expansion of (peg) interferon therapeutic indications, and the number of patients with chronic hepatitis exposed to (peg) interferon, other antivirals, and granulocyte growth factors.

With regard to the management of psoriasis in these special hosts, the Dermatologist needs to be involved as soon as possible in order to obtain an early diagnosis (possibly confirmed by histopathology), to take into account differential diagnoses of HCV-infected patients receiving multiple pharmacological treatments and with non-infrequent co-morbidities (i.e. HIV disease), and to monitorize patients over treatment and over time³⁴. According to existing evidences, also in HCV-infected patients with a newly recognized psoriasis or with an exacerbating psoriatic disease, cyclosporin seems a suitable treatment, with times and modes of delivery tailored on every single patient and disease presentation and evolution, as recently commented by Imafuku and coworkers³⁵: the cyclosporin treatment, as in our case, is usually effective and well tolerated, compared with that with systemic steroids. However, also novel-generation compounds (like etanercept) are expected to play a significant role in the next future, since they act on the activated component of TNF-alpha which may have a remarkable part in the pathogenesis and treatment of HCV disease itself, complicated by psoriasis³⁶. Recently, a HIV-HCV co-infected man had his psoriatic arthropathy refractory to cyclosporine A and methotrexate successfully treated with etanercept, which is gaining a strong rationale for an effective management of these associated disorders³⁶.

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