Case Report

Severe Stomatitis Complicating Treatment With Pegylated-Interferon α-2a and Ribavirin in an HCV-Infected Patient

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Objective: To report a case of severe stomatitis probably induced by peginterferon α-2a.

Methods and Results: A 42-year-old man with chronic hepatitis C genotype 1b commenced treatment with peginterferon α-2a 180 μg subcutaneously weekly and ribavirin 1000 mg/d orally. Twenty-eight days after commencing treatment, the patient experienced difficulties with swallowing, dryness of the mouth, stomatitis, and pain. Diagnosis of stomatitis was made. He did not complain of any other adverse effect of peginterferon α-2a and ribavirin. Both medications were discontinued. The withdrawal of peginterferon α-2a was followed by the resolution of the oral lesions in three weeks. The patient was followed up in the outpatient clinic at one month and at three months, and he was asymptomatic.

Conclusions: Manufacturers of peginterferon α-2a suggest that mouth ulceration, stomatitis, dysphagia, and glossitis are considered adverse reactions of this medication. In this case, the most likely cause of the stomatitis was considered to be peginterferon α-2a because of the close temporal relationship between exposure to the drug and onset of symptoms, as well as the rapid resolution of the symptoms and signs after peginterferon α-2a was discontinued. An objective causality assessment revealed that a adverse drug event was possible. Clinicians should be aware of this potentially adverse effect of a widely used drug.

Key Words: adverse drug reaction, chronic hepatitis C, peginterferon α-2a, ribavirin stomatitis

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In recent years, treatment of chronic hepatitis C infection (HCV) has significantly improved, including the introduction of peginterferon (PEG-IFN). PEG-IFN is a pegylated formulation of recombinant human interferon α (IFN-α) conjugated with molecules of polyethylene glycol. The major advantages of this formulation, compared with standard, non-pegylated IFN-α, are[1] a prolonged half-life, which allows for once-weekly injection and[2] high and stable serum concentrations of the molecule. Two forms of PEG-IFN, α-2a and α-2b, have been approved for HCV treatment. Although they differ in their pharmacologic properties, both possess an increased and sustained duration of activity due to longer serum half-lives than conventional IFN-α.[1]

Combination therapy with PEG-IFN and ribavirin yields higher response rates, with eradication of the virus in more than half of treated patients. Sustained virologic response is achievable in nearly half of patients with genotype 1 and about 80% of those with genotypes 2 and 3.[2] The importance of adherence to anti-HCV therapy and dose maintenance of PEG-IFN and ribavirin to maximize sustained virologic response rates has become more apparent. The principal adverse effect of ribavirin is hemolytic anemia. Adverse effects associated with PEG-IFNs include fatigue, influenza-like symptoms, gastrointestinal disturbances, hematological abnormalities, neuropsychiatric effects (particularly depression),

Key Points

- Severe stomatitis can possibly be induced by peginterferon α-2a.
- The overall risk of severe oral complications during the use of peginterferon α-2a appears low; clinicians should be aware of this rare reaction.
- Early detection and appropriate management of adverse side effects during peginterferon and ribavirin therapy for HCV allow optimizing adherence and virological efficacy.

and thyroid dysfunction.[3,4] The development of oral adverse drug reactions is rare. Severe stomatitis may rarely be triggered by PEG-IFNs therapy in HCV patients. We report the case of a man who developed symptoms and signs of severe stomatitis during therapy with PEG-IFN α-2a and ribavirin for chronic HCV.

Case Report

A 42-year-old man with chronic hepatitis C genotype 1b and metavir stage 3 hepatic fibrosis presented with difficulties on swallowing, dryness of the mouth, stomatitis, and pain. Three years prior, chronic HCV was diagnosed on the basis of detectable anti-HCV antibodies and elevated serum alanine aminotransferase levels. He commenced treatment with peginterferon α-2a 180 μg subcutaneously weekly and ribavirin 1000 mg/d orally. His baseline HCV viral load was 1191150 copies/mL. Twenty-eight days after commencing treatment, the patient experienced difficulties with swallowing, dryness of the mouth, difficulty in chewing, and pain. Examination of oral cavity showed painful aphthous ulcerations and inflammation of the oral mucosa and tongue. The lesions varied in size from 0.5 cm to 2.5 cm and in number from 5 to 10. Diagnosis of stomatitis was made. There were no extra oral signs. There was no bone marrow suppression either or any other condition, such as neutropenia and fever. The patient had not experienced stomatitis aphthosa or oral herpes before. He did not complain of any other adverse effect of peginterferon α-2a and ribavirin. Laboratory tests showed no abnormalities in white blood cells or hemoglobin or in kidney function. He had no history of cigarette smoking or substance abuse and denied the use of any other drugs or herbal remedies. He had undergone no recent dental work and had no specific dental problems. No other systemic or other cause of mouth ulcers, such as deficiencies of folic acid or iron, deficiencies of vitamin B_1, B_2, B_6, or B_{12}, or Sweet syndrome, could be detected. PEG-IFN α-2a and ribavirin were discontinued. The withdrawal of both medications was followed by the resolution of the oral lesions in three weeks. The patient was followed up in the outpatient clinic at one month and at three months, and he was asymptomatic.

Discussion

A wide spectrum of drugs can sometimes give rise to numerous adverse orofacial manifestations, particularly dry mouth, taste disturbances, oral mucosal ulceration, and/or gingival swelling. The most common reactions are dry mouth, taste disturbances, and gingival swelling. Drug-induced oral mucosal ulceration is also not uncommon, particularly in cancer chemotherapy. Stomatitis is an inflammation of the oral mucosa, due to local or systemic factors, which may involve the buccal and labial mucosa, palate, tongue, floor of the mouth, and the gingivae. The etiology of medication-induced stomatitis is unclear. It can be caused by direct mucosal contact with medication (contact stomatitis), but this seems unlikely, as patients have given no history of keeping the medications for a long time in the mouth. The reaction could be a systemic allergic reaction. Mucosal contact with high concentrations of potassium chloride, pancreatic enzymes, aspirin, and cocaine are known to cause oral lesions.[5] The profile of adverse drug reactions (ADRs) of interferon plus ribavirin has been well described.[6,7] Two clinical trials compared the efficacy and safety profile of peginterferon α-2a or α-2b monotherapy versus standard interferon monotherapy and suggested a qualitatively similar profile of ADRs, and no previously unknown ADR was found with peginterferon.[8,9] However, results of two other studies investigating peginterferon α-2a or α-2b plus ribavirin suggest differences in the frequency of some ADRs compared with that of standard interferon plus ribavirin.[10] The principal adverse effect of ribavirin is hemolytic anemia. Adverse effects associated with IFN-α and PEG-IFNs include fatigue, influenza-like symptoms, gastrointestinal disturbances, hematological abnormalities, neuropsychiatric effects (particularly depression), thyroid dysfunction, and dermatologic effects, such as alopecia and pruritus.[11] Manufacturers of peginterferon α-2a suggest that mouth ulceration, gingival bleeding, stomatitis, dysphagia, and glossitis are considered adverse reactions of this medication. A search of MEDLINE (1966-March 2007) was conducted to evaluate the published literature on interferon-induced stomatitis. Reference lists from relevant papers were used to identify additional articles. This search strategy revealed two cases that suggested an association between stomatitis or oral ulcerations and interferon therapy. Qaseem et al reported a case of a patient who received α interferon for non-A, non-B, and non-C chronic hepatitis and developed severe painful oral ulcerations associated with inanition and weight loss.[12] Dalekos et al[13] described a 62-year-old woman with chronic active HCV infection in treatment with interferon-α2b at a dose of 3 million units subcutaneously three times per week. Tens month later, the patient developed aphthous stomatitis and claimed intense pain. She discontinued the treatment, with subsequent resolution of the stomatitis.

Analysis of our case suggests a relationship between exposure to peginterferon α-2a and the development of stomatitis. There was a temporal relationship between the development of symptoms after starting peginterferon α-2a therapy. The presentation was atypical of herpetic disease progression, and medication-induced stomatitis was considered. Other potential causes of stomatitis were ruled out. Our patient did not receive concomitantly other immunosuppressant drugs, which should be considered an additional contributing factor in masking the development of stomatitis. When peginterferon

α-2a was discontinued, her symptoms improved and resolved quickly. This fact was similar to two of the cases reported in the literature. In our patient, based on the Naranjo probability scale, peginterferon α-2a could be considered the possible cause of the stomatitis.[14]

Adherence to standard combination therapy and maintaining the doses of peginterferon and ribavirin are now recognized as critical to maximizing a sustained virologic response rate, particularly in patients infected with genotype 1 and patients who demonstrate an early virologic response. Treatment-related side effects that are most likely to result in dose reductions or discontinuation might also play a role in successful adherence to therapy and achieving a sustained virologic response, as side effects are the primary reason for nonadherence. Our patient developed severe stomatitis, and due to this adverse drug reaction, he did not correctly take the medication regimen.

Although the overall risk of severe oral complications during the use of peginterferon α-2a appears low, clinicians should be aware of this rare reaction. Early detection and appropriate management of adverse side effects during peginterferon and ribavirin therapy for HCV allow optimizing adherence and virological efficacy. In patients who develop severe stomatitis, clinicians should manage these patients with caution. Rechallenged treatment should be prescribed in cases where severe activity of HCV and severe fibrosis are present.

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—Walt Whitman