ADVANCES IN HEPATOLOGY

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Diagnosis and Management of Telaprevir-Associated Rash

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G&H How common is rash among patients treated with telaprevir?

EL The safety data for telaprevir (Incivek, Vertex) show that rash occurs in 56% of patients treated with telaprevir, compared to 34% of patients treated with peginterferon and ribavirin alone. Similarly, pruritus has been reported in 47% of patients who received telaprevir-based triple therapy, compared to 28% of patients treated with peginterferon and ribavirin.

In most cases, this rash is mild or moderate. Severe rash—defined as a generalized rash, a rash with vesicles, or a rash with bullae or ulcerations—was reported in only 4% of telaprevir-treated patients and less than 1% of patients treated with peginterferon and ribavirin. Treatment discontinuations due to rash were also rare; 6% of patients had to stop telaprevir but continued peginterferon and ribavirin, and 1% of patients had to stop all medications. Overall, rash is a frequent side effect of telaprevir, but it is not frequently severe, and it rarely limits patients' duration of exposure to the protease inhibitor.

G&H Why is telaprevir-associated rash a potentially serious side effect?

EL The most frequent rash associated with telaprevir therapy is a simple, mild rash that does not represent a serious side effect. However, a very small percentage of telaprevir-associated rashes have progressed to serious skin reactions, including drug rash with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS). The percentage of patients with DRESS is not reported in the telaprevir package insert, but SJS has been reported in less than 1% of patients. DRESS comprises a constellation of symptoms including rash with fever and facial edema and evidence of organ involvement: increased levels of liver enzymes, a decrease in kidney function, and/or nephritis or hepatitis.

Mild rashes can be treated with topical steroids and antihistamines; however, if a rash becomes severe and progressive, it is necessary to stop telaprevir or, more rarely, to stop all 3 medications. A severe, progressive rash can become a serious medical problem if correct action is not taken. The clinician should be vigilant in this regard, monitor for progressive rash, and ensure that the rash responds appropriately to the therapy that is delivered. If the rash progresses and becomes severe despite treatment, then telaprevir should be discontinued; subsequently, if there is still no improvement, ribavirin and peginterferon should also be discontinued.

G&H What does a telaprevir-associated rash look like?

EL A mild telaprevir-associated rash is a fairly typical maculopapular rash (Figure 1). It is difficult to differentiate mild rash due to telaprevir from mild rash due to ribavirin. These mild rashes are not typically raised, but they can be pruritic.

A moderate telaprevir-associated rash consists of some confluence of diffuse red spots (Figure 2). This rash can have some texture, and it can also appear somewhat eczematous, almost as though it has some crusty material on it.

A severe telaprevir-associated rash is a further confluence of many of these reactions (Figure 3). It can be somewhat raised. This rash consists of areas of red lesions that enlarge and grow together, and they can eventually cause redness over a large part of the body. This rash is certainly different in appearance than a ribavirin-associated rash; a telaprevir-associated rash is more focal, with red patches that grow together, as opposed to a ribavirin-

Figure 1. A mild rash associated with telaprevir therapy. Photo courtesy of Vertex Pharmaceuticals.

Figure 2. A moderate telaprevir-associated rash. Photo courtesy of Vertex Pharmaceuticals.

Figure 3. A severe rash associated with telaprevir. Photo courtesy of Vertex Pharmaceuticals.

associated rash, in which a maculopapular appearance is more common.

G&H Has rash been associated with boceprevir?

EL No, rash has not been associated with boceprevir (Victrelis, Merck). In treatment-naïve patients, rash occurred in 17% of patients treated with boceprevir-based triple therapy compared to 19% of patients treated with peginterferon and ribavirin. In the boceprevir re-treatment trial, rash occurred in 16% of patients treated with boceprevir-based triple therapy compared to 6% of patients who received peginterferon and ribavirin. There is clearly not an increased frequency of rash among patients treated with boceprevir-based therapy.

It is interesting that rash is associated only with telaprevir, but currently this difference cannot be explained. Once we understand the etiology of the telaprevir rash, it may become clear why telaprevir causes rash and boceprevir does not. Understanding the mechanism behind telaprevir-associated rash is a current focus of research, but the pathophysiology of this rash is not understood at this time.

G&H How should a telaprevir-associated rash be managed?

EL For a patient with a self-limited, mild rash on a small area of the body, clinicians should consider the administration of antihistamines and topical steroids. If that therapy does not work and the rash continues to progress and becomes severe, then the clinician should stop telaprevir. In general, when telaprevir is stopped, the rash will improve; it may take a few weeks, but it should resolve completely.

If there is no improvement within 7 days after stopping telaprevir, or there is not enough improvement, then it may be necessary to stop ribavirin. If the rash is severe and continues to progress, then all medications should be

stopped. If telaprevir has been stopped, then oral corticosteroids can be administered, if necessary, particularly for treatment of severe rash.

G&H If it is necessary to stop telaprevir, can this drug be restarted once the rash resolves?

EL No, once you stop telaprevir, you should not restart therapy with this medication. Once you stop telaprevir, you should simply complete the treatment course with peginterferon and ribavirin. Fortunately, telaprevir is only administered for 12 weeks, so even if you have to stop telaprevir early, you have likely achieved much of your goal of viral suppression.

G&H Do you feel that the rash associated with telaprevir limits the drug's overall utility?

EL No. Although telaprevir-associated rash has been the subject of much discussion, only 6% of patients must discontinue telaprevir because of rash, and only 4% of patients develop a severe rash. For patients who develop a mild or moderate rash, clinicians can simply treat it and continue telaprevir through Week 12 as planned, then complete the course of therapy with peginterferon and ribavirin.

The situation that poses the greatest risk is if a patient develops a telaprevir-associated rash but clinicians do not recognize it as such. If a patient develops a ribavirin-associated rash and treatment is continued, there are generally few consequences. With a telaprevir-associated rash, however, continuing telaprevir despite a progressive rash puts the patient at risk for a severe rash or even a rash with systemic consequences, such as DRESS or SJS. Thus, it is important that clinicians discontinue telaprevir if a patient has a severe rash.

While there is a potential for rash to be a serious side effect with telaprevir, most rashes that are seen with this drug are mild and easily managed. Certainly, improvement in sustained viral response of 33% with telaprevir-based therapy compared to standard therapy with peginterferon and ribavirin is a major step forward in the treatment of patients with chronic hepatitis C virus infection. Overall, clinicians should consider the risk of telaprevir-associated rash in the context of the benefit this medication provides.

G&H What further research is needed regarding telaprevir-associated rash?

EL The largest unanswered question is the pathophysiology of this rash. Once we understand the etiology of the rash, we may be able to find alternative management strategies that may be useful. It would also be helpful to learn if there were baseline characteristics that might predispose or predict which patients are at risk for a severe rash. I would hope that much effort is being put forth to determine if there are any patient characteristics that might put certain individuals at particular risk for development of rash. If identified, these risk factors would allow us to take better care of our patients.

Suggested Reading

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