ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Risk of Autoimmune Complications Associated with Interferon Therapy

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G&H Which autoimmune conditions have been observed in hepatitis C virus–infected patients who are being treated with interferon?

MOS Many autoimmune conditions have been observed in this setting. Clinicians should be very careful when using interferon in hepatitis C virus (HCV)-infected patients with superimposed autoimmune disorders, as interferon can exacerbate these autoimmune conditions. Common autoimmune diseases that can be exacerbated by interferon include rheumatoid arthritis, psoriasis, vitiligo, hypothyroidism, hyperthyroidism, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, myasthenia gravis, Addison disease, celiac disease, polymyositis, and superimposed autoimmune hepatitis. These are the most common autoimmune conditions clinicians may encounter, but any autoimmune disease could potentially be superimposed on HCV infection.

G&H How often does interferon exacerbate a preexisting autoimmune condition?

MOS Fortunately, this scenario occurs in only 4% of cases, the majority of which involve thyroid dysfunction, followed by psoriasis and rheumatoid arthritis. Much less frequently, other severe autoimmune diseases have also been reported, such as systemic lupus erythematosus.

G&H Do certain factors increase the risk that interferon will cause or exacerbate an autoimmune condition?

MOS We have no way to predict the development of de novo autoimmune disease secondary to interferon therapy. However, a good questionnaire and a thorough patient history can help clinicians identify any preexisting autoimmune diseases that might be exacerbated by interferon treatment. One of the biochemical markers of autoimmune diseases is the presence of high serum gammaglobulin levels. Thus, if patients have high levels of serum gammaglobulins prior to treatment, or they develop increased levels of gammaglobulin while on treatment, clinicians should then consider the possibility that the patients may develop an autoimmune disorder. Similarly, the presence of serum autoantibodies, such as antinuclear antibodies or thyroid autoantibodies, prior to interferon therapy may also predict the future development of autoimmune hepatitis or Hashimoto thyroiditis.

G&H Why does interferon exacerbate autoimmune conditions?

MOS Interferon-α has 2 main mechanisms of action: straightforward antiviral activity and induction of cellular and innate immune responses. Interferon's direct antiviral actions include the induction of several genes and proteins that ultimately create the antiviral status of infected cells. Among these proteins, protein kinases and 2'5' oligoadenylate synthetase have been reported to be the most important. Interferons also induce expression of major histocompatibility complex, both on antigen-presenting cells (APCs) and hepatocytes, resulting in virus-specific lysis of infected cells mediated by a cytotoxic T-cell response.

In almost all autoimmune diseases, there is evidence for the role of environmental factors, particularly viral infection and increased numbers of circulating autoreactive T cells and B cells. Endogenously produced or thera-

peutically applied interferon-α can increase activation of these autoreactive cells via a vast array of mechanisms. Interferon-α induces numerous target genes in APCs, such that APCs are stimulated and enhance humoral autoimmunity, promote isotype switching, and potently activate autoreactive T cells. Moreover, interferon-α can synergistically amplify T-cell autoreactivity by directly promoting T-cell activation and keeping activated T cells alive. Via the latter mechanisms, interferon can trigger autoimmune diseases in patients who have an underlying predisposition to develop these conditions.

G&H Does interferon-α 2a differ from interferon-α 2b in regard to its effect on the innate immune response?

MOS One important difference between interferon-α 2a and interferon-α 2b is the size of the polyethylene glycol molecule that is attached to the interferon when it is pegylated. When interferon-α 2a is pegylated, it is attached to a polyethylene glycol molecule that is 40 kD in size. In contrast, interferon-α 2b is attached to a polyethylene glycol molecule that is only 12 kD in size. The difference in size between these polyethylene glycol molecules predisposes different exposure to interferon and different induction of interferon-inducible genes among the 2 pegylated molecules, probably predisposing differences in the occurrence of autoimmune disorders.

G&H Can an autoimmune condition occur in a patient receiving interferon in the absence of a preexisting autoimmune condition?

MOS In the early 1990s, there was a report in the literature of a patient with hepatitis B virus infection who developed Hashimoto thyroiditis in the absence of an underlying autoimmune condition. Another case reported a patient who developed chronic autoimmune hepatitis under similar circumstances. These reports show that patients do not need to have an underlying autoimmune condition in order to develop an autoimmune response during interferon therapy. Such a response will certainly occur more frequently in patients who have preexisting autoimmune conditions, but autoimmune complications can occasionally develop de novo.

G&H Have any studies assessed the development of autoimmune conditions among interferon-treated patients?

MOS Yes, several studies have examined autoimmune conditions in these patients. Older studies in patients with chronic HCV infection demonstrated that the most common autoimmune disorder associated with interferon therapy is hypothyroidism. However, these studies were conducted more than 8 years ago. As the possibility of interferon-free HCV therapy has advanced, interest in the phenomenon of interferon-induced autoimmune reactions has declined, and researchers are no longer actively investigating this issue.

G&H What factors should clinicians consider when weighing the risks and benefits of interferon treatment?

MOS Clinicians should consider both the severity of the patient's HCV infection and his or her autoimmune background. If the patient has mild chronic hepatitis and/or a strong autoimmune background, then treatment should be delayed until oral interferon-free HCV therapy becomes available. On the other hand, if the patient has advanced liver disease and/or an autoimmune background that is not significant, then the clinician could proceed with treatment and take the risk of developing a mild autoimmune reaction. Again, this decision depends significantly on the autoimmune background of the patient; if a patient has mild rheumatoid arthritis, then interferon therapy may be worth the risk. If the patient has an autoimmune hemolytic anemia and cardiomyopathy due to coronary artery disease, however, then interferon therapy would probably be too risky.

G&H Can clinicians reduce the risk that interferon will exacerbate a preexisting autoimmune condition?

MOS There is really no way to reduce this risk, but clinicians can try to minimize the consequences of such an exacerbation. For example, research has shown that females are more prone to develop hypothyroidism, especially if they have preexisting thyroid autoantibodies. To mitigate this risk, clinicians should test monthly for thyroid-stimulating hormone and start treatment as soon as patients begin to develop hypothyroidism. For patients with psoriasis, clinicians should stress the importance of avoiding sun exposure while they are receiving interferon, as sun exposure may enhance skin reactions due to interferon or ribavirin. For patients with cryoglobulinemia or rheumatoid arthritis, clinicians should simply be alert to the possible development of an autoimmune complication and treat it early if it occurs.

G&H What further research is needed regarding the use of interferon in patients with autoimmune disease?

MOS Ideally, researchers could conduct clinical trials to evaluate what happens when interferon is administered

to patients with autoimmune disorders, but the risk of serious adverse events associated with this treatment has precluded such studies. Likewise, I would like to know whether a specific human leukocyte antigen allele is more common in patients who develop autoimmune complications; however, conducting such a study is practically impossible because of the very large number of patients who would need to be included in such a study.

G&H Are there any alternative HCV treatments that clinicians might consider if they are concerned about the risks associated with interferon?

MOS Yes. Over the next 5 years, I believe many new options for HCV therapy will become available, including both new interferons with fewer side effects (eg, λ interferon), as well as interferon-free regimens. For example, both of the interferons currently on the market are subtypes of interferon-α, but a new type of interferon with milder side effects is currently being developed, which could offer an alternative for patients who are intolerant to interferon-α–based therapy. In addition, new HCV protease and polymerase inhibitors and other new drugs are being tested in combinations that would not require interferon as part of the treatment regimen.

Thus, patients who are intolerant to interferon-α and who do not have advanced liver disease may want to wait until they can receive a different type of interferon or an interferon-free regimen; hopefully, such options will be available in approximately 4–5 years, and patients with mild HCV infection will not progress significantly during that time. This concept of delaying therapy while waiting for new medications, called warehousing, is certainly appropriate for patients with mild chronic hepatitis who are intolerant to interferon.

G&H Given that interferon-free regimens are already in development, how should today's clinicians manage patients who are at risk for an interferon-induced autoimmune reaction?

MOS The possibility of having interferon-free HCV treatment regimens is very exciting and perhaps overdue, given that interferon was discovered in the 1950s. Fortunately, clinical trials of interferon-free regimens are currently underway. Once an interferon-free treatment option becomes available, clinicians will no longer need to worry about the patient's autoimmune background.

Having interferon-free regimens on the horizon gives today's hepatologists the option to delay treatment in certain patients. For patients with very mild chronic hepatitis and a preexisting autoimmune condition, delaying therapy is a better option than risking that interferon therapy might trigger the development of a serious autoimmune disease. Currently, I elect to postpone therapy in approximately 20% of patients who present for HCV treatment; this group includes not only patients with autoimmune diseases but also those who have other reasons for avoiding current HCV treatment regimens. In these patients, I perform an ultrasound every year to check whether their liver disease is progressing; if the disease remains stable, then these patients can continue to be monitored until an interferon-free oral regimen becomes available.

Suggested Reading

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