ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Current Advances in the Treatment of Autoimmune Hepatitis

Albert J. Czaja, MD
Professor of Medicine
Mayo Clinic College of Medicine

G&H What are the typical characteristics of autoimmune hepatitis?

AC Autoimmune hepatitis has been recognized since the 1950s. Originally, it was described in young women with a phenotype that included obesity, acne, round facies, amenorrhea, and cirrhosis. When it was first recognized, autoimmune hepatitis was highly fatal; 50% of patients died within 3 years. Since that time, the diagnosis has been refined, in part due to the identification of serologic markers to exclude viral (eg, hepatitis A, B, and C infections), hereditary (eg, Wilson disease), and other immune conditions (eg, primary biliary cirrhosis and primary sclerosing cholangitis). Furthermore, drugs that can induce a clinical syndrome like autoimmune hepatitis are now recognized and properly monitored (eg, minocycline and diclofenac) or have been eliminated from clinical practice (eg, oxyphenisatin).

Autoimmune hepatitis was initially called "lupoid hepatitis" because it shared serologic features with systemic lupus erythematosus and it was thought to evolve into that disease. This transition was subsequently discounted, and autoimmune hepatitis is now recognized as a valid subtype of chronic liver disease. It is characterized by major elevations of serum aminotransferase levels, hypergammaglobulinemia, interface hepatitis on histological examination, and autoantibodies. Interface hepatitis is the hallmark of the disease, and the presence of plasma cells within the inflammatory infiltrate strengthens the diagnosis (Figure 1). Panacinar (lobular) hepatitis and even centrilobular zone 3 necrosis have also been included in the histological spectrum. Diagnostic criteria have been codified to emphasize these aspects and to indicate its hepatitic rather than cholestatic nature.

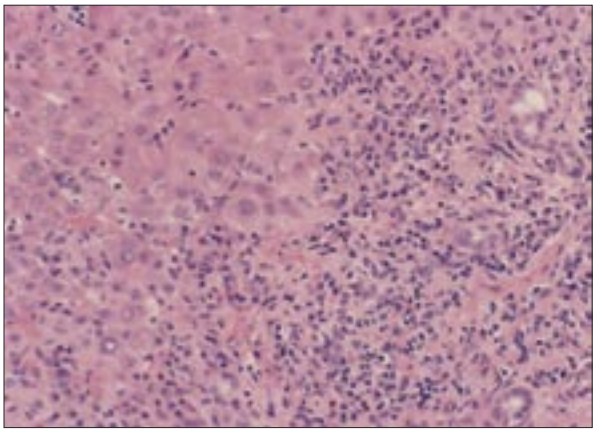

Figure 1. Interface hepatitis with plasma cell infiltration. The limiting plate of the portal tract is broadly disrupted with extension of the mononuclear infiltrate into the hepatic lobule. Cells with dense nuclei bordered by cytoplasmic halos constitute plasma cells. The features of interface hepatitis and plasma cell infiltration support the diagnosis of autoimmune hepatitis. Hematoxylin and eosin, ×200.

G&H What are some of the markers that have been identified?

AC Serologic markers that support the diagnosis are antinuclear antibodies, smooth muscle antibodies, and antibodies to liver-kidney microsome type 1. There are other serologic markers that must be assessed to secure the diagnosis by their absence, including assays for viral infection (hepatitis A, B, and C viruses) and antimitochondrial antibodies (primary biliary cirrhosis). New serologic markers continue to be characterized in the hope of improving diagnostic specificity and prognostic value. Antibodies to soluble liver and liver-pancreas antigens and antibodies to the asialoglycoprotein receptor have this promise.

G&H What is the initial therapeutic approach?

AC The high mortality of severe autoimmune hepatitis stimulated the search for effective treatments. Initial strategies focused on corticosteroids, particularly prednisone, which has demonstrated clear benefit due to its ability to normalize laboratory tests, improve symptoms, and prolong immediate survival. Subsequently, treatments were

refined by the addition of azathioprine, a corticosteroid-sparing agent. Today, azathioprine and prednisone are the preferred treatments for autoimmune hepatitis, and they are associated with a 20-year survival rate that exceeds 80%. Liver transplantation has emerged as a life-saving therapy for decompensated disease, and transplanted patients have a 10-year actuarial survival rate of 75%.

G&H Are there problems with the current treatment strategies?

AC The major problem with the corticosteroid regimens has not been failure to suppress inflammatory activity, prevent disease progression, or prolong survival. The principal difficulties have related to the quality of life while on therapy and the prospect of indefinite treatment. There has always been concern about stopping treatment because the disease relapses after drug withdrawal in 20–86% of patients and re-treatment with corticosteroids is frequently necessary. Prolonged or repeated therapies with the corticosteroid regimens are associated with side effects in as many as 70% of individuals. These side effects are typically cosmetic, including weight gain, facial rounding, acne, and striae, but osteopenia, osteoporosis, and vertebral compression are possibilities. Certain other consequences, such as diabetes, hypertension, emotional lability, or even frank psychosis, may also occur. Some of the corticosteroid-induced side effects may be difficult to distinguish from symptoms associated with the liver disease itself, but their occurrence typically justifies reductions in the corticosteroid dose or substitution of the drug with a nonsteroidal medication, such as high-dose azathioprine in (2 mg/kg daily). Efforts to adjust therapies and find alternative treatment strategies stem from these difficulties. In addition, the current standard treatment is effective in suppressing the disease, but it typically does not cure the condition.

G&H What are the current treatment outcomes for patients with autoimmune hepatitis?

AC Clinical, laboratory, and histologic remission occurs in 80% of patients after 3 years of treatment, but this improvement may not be sustained after drug withdrawal. If all manifestations of the disease can be completely resolved, including the laboratory abnormalities and symptoms, and the liver architecture can be returned to normal, a sustained long-term remission after initial treatment is possible in 21% of patients. Treatments to these complete endpoints, however, can be protracted and in some patients not achievable. Re-treatment after relapse to the same endpoint can induce a sustained long-term remission in another 28% of patients. The probability of a sustained remission after initial or repeated treatments is 47% after 10 years. Most patients are on continuous or repeated treatments.

Nine percent of patients deteriorate despite compliance with therapy (treatment failure); 13% develop intolerable side effects; and 13% improve but not to a degree to satisfy remission criteria. These latter patients have an incomplete response, and they require continuous therapy. Histological cirrhosis may develop in 40% of treated patients after 10 years, but they typically do not have decompensated disease or shortened survival. The development of ascites in these patients is usually the first indication that liver transplantation is necessary. Progression to cirrhosis during therapy is a manifestation of aggressive disease, and these patients typically relapse after drug withdrawal.

Patients who relapse respond rapidly and completely to re-treatment. Relapse that is properly monitored does not result in treatment resistance or disease progression, but it can lead to treatment dependence. The major consequence of relapse and re-treatment is the development of drug-related side effects. Long-term maintenance schedules can diminish these consequences by using low-dose prednisone schedules (<10 mg daily) or azathioprine only (2 mg/kg daily). The low-dose treatment regimens are intended to suppress rather than eradicate the disease. The liver disease on these schedules can become inactive, and attempts should be made periodically to reduce the dose of medication or to discontinue the drug. This withdrawal challenge may be rewarded by an ability to permanently discontinue the medication.

G&H Has increased understanding of autoimmune hepatitis led to the development of new therapies?

AC Yes, in part the emergence of new treatment strategies relates to advances in our understanding of the mechanisms of the liver disease. The emergence of new powerful immunosuppressive agents from the transplantation experience has also contributed to therapeutic progress. The costimulatory signals that activate the immunocytes that subsequently differentiate and infiltrate the liver have now been defined as have the factors that influence the proliferation and perpetuation of these activated, liver-infiltrating cells. These advances in knowledge have provided opportunities for the development of focused, site-specific, pharmacologic and molecular interventions.

G&H What are some of the new strategies being evaluated?

AC Many of the newest agents have emerged from the experience in liver transplantation. These drugs have more powerful immunosuppressive and site-specific actions

than either prednisone or azathioprine. The largest clinical experience has been with the calcineurin inhibitors. These medications inhibit activation of the nuclear factors, particularly nuclear factor kappa B, that modulate cytokine production. In turn, the differentiation and proliferation of activated immunocytes are impaired. The two calcineurin inhibitors that have been evaluated in autoimmune hepatitis are cyclosporine and tacrolimus. The clinical experience with each is limited, and neither has been incorporated into conventional treatment algorithms. Cyclosporine has had the largest clinical use, and it has been administered as a first-line therapy in treatment-naive patients and as a salvage therapy in patients who have been refractory to the conventional schedules or intolerant of the conventional medications.

In pediatric patients, the goal has been to avoid corticosteroids because it can impair growth dynamics in the prepubertal child and produce intolerable cosmetic changes in the adolescent. Cyclosporine has been used over a 6-month period as front-line therapy in children before being replaced by conventional corticosteroid schedules. During this short exposure, indices of liver inflammation improved, growth dynamics were maintained, and the medication was well tolerated. In adults, several clinical experiences have demonstrated that cyclosporine can improve the serum aminotransferase abnormalities and significantly improve the histologic features of the disease. Patients with autoimmune hepatitis who have been questioned on their acceptance and tolerance of the different treatment options have preferred cyclosporine. Cyclosporine has not yet been compared directly to conventional therapy, and its use in autoimmune hepatitis is still empiric. The drug does have promise, but it must be evaluated in a more rigorous fashion.

Mycophenolate mofetil (CellCept, Roche) has also been used in the treatment of autoimmune hepatitis. This agent is a purine antagonist, and it inhibits the production of nucleotides that are important in the synthesis of new DNA and the proliferation of lymphocytes. Azathioprine is also a purine antagonist, but mycophenolate has more specific actions and a different metabolic pathway. Mycophenolate mofetil does not depend on thiopurine methyltransferase for its elimination.

G&H Has mycophenolate been studied in clinical trials?

AC Mycophenolate has not been compared to conventional therapies; however, there are reports from three small clinical experiences that it improves laboratory tests of liver inflammation, reduces histologic abnormalities, and is well tolerated. A particular advantage was the opportunity to reduce the dose or discontinue the use of prednisone in many patients. Mycophenolate is expensive, approximately $700 per month; treatment may be indefinite; and the drug is not established as a superior therapy for autoimmune hepatitis. Consequently, its use should be restricted until studies document its efficacy and define its target population.

G&H What other agents have been studied in the treatment of autoimmune hepatitis?

AC Sirolimus (Rapamune, Wyeth), an mTOR (mammalian target of rapamycin) inhibitor, has site-specific activity, although clinical experience in autoimmune hepatitis is still very limited. Sirolimus modifies the cytokine milieu, preventing sensitized immunocytes from differentiating into cytotoxic T cells that infiltrate the liver. In contrast to calcineurin inhibitors and purine antagonists, which inhibit lymphocyte proliferation, sirolimus seems to affect the differentiation of immunocytes after their activation.

G&H Are any of these agents being evaluated in combination?

AC Since each of the agents described above has site-specific activity, the combination of drugs with complementary actions is feasible. However, this concept has not yet been tested in a meaningful way. The combination of a calcineurin inhibitor, such as cyclosporine, with sirolimus would be an example of a complementary regimen with dual actions. The International Autoimmune Hepatitis Group, a body of clinicians and scientists with a career focus on autoimmune hepatitis, has outlined treatment strategies that are worthy of study, and it could serve as a investigational network to study new treatments quickly and well. The National Institutes of Health have also encouraged the development of collaborative investigational teams as the best mechanism to introduce new treatments. Mycophenolate, calcineurin inhibitors, sirolimus, and various combination therapies are promising new options for refractory or steroid-dependent disease, and these regimens are prime candidates for study in a collaborative fashion.

G&H What molecular interventions are being explored?

AC There are several potential molecular interventions for autoimmune hepatitis (Figure 2). Blocking peptides can be synthesized to compete with the disease-producing antigen for presentation by the class II molecules of the major histocompatibility complex. These peptides can occupy the antigen-presenting sites with a false antigen and thereby prevent lymphocyte activation. This strategy has been used successfully in rheumatoid arthritis.

Another strategy is to use a molecule that impairs the activation of immunocytes directly at their interface with antigen-presenting cells. This molecule, cytotoxic T lymphocyte antigen-4, blocks the second costimulatory signal

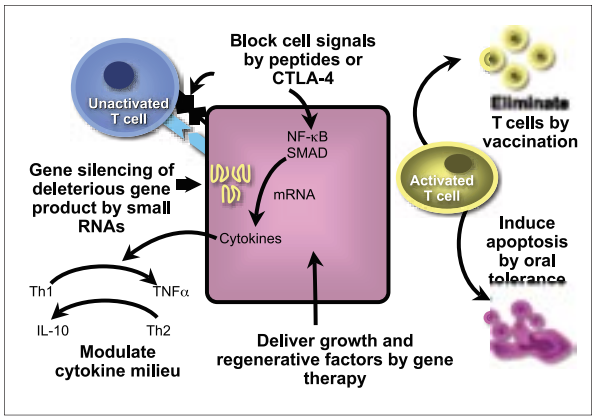

Figure 2. Feasible site-specific molecular interventions for the treatment of autoimmune hepatitis. Gene-silencing inhibitory RNAs, cytokine manipulations, gene therapies, oral tolerance induction, T-cell vaccination, and inhibition of the costimulatory signals for immunocyte activation by blocking peptides or cytotoxic lymphocyte antigen-4 (CTLA-4) are theoretical options worthy of further investigation.

necessary for immunocyte activation, and it has been used with some success in the treatment of patients with mismatched bone marrow transplants. Another intervention is to desensitize cells to the triggering antigen through the induction of oral tolerance. With this strategy, patients ingest the antigen that causes the disease. This approach has been used in several immune-mediated diseases. Low doses of the ingested antigen generate production of cytokines that suppress the immune response, whereas high doses of the ingested antigen induce apoptosis of the cytokine-producing cells and cause anergy. Treatment trials await the appropriate animal model and characterization of the critical epitope that activates the disease.

T-cell vaccination is another promising strategy which has been tested only in animal models of experimental autoimmune hepatitis. Here, the activated T cells that cause liver destruction are harvested from the spleens of afflicted animals, inactivated through radiation, and then reinfused into susceptible or afflicted animals. T-cell vaccination prevents the disease in susceptible animals and attenuates it in animals already afflicted. Identification of the specific clone responsible for the disease is required to precisely target this therapy.

Recombinant technology now makes manipulation of the counter-regulatory cytokines possible. Polymorphisms of the gene producing tumor necrosis factor-α may favor a type 1 cytokine response and liver cell destruction in autoimmune hepatitis, whereas interleukin 10 may favor an anti-inflammatory, counter-regulatory, type 2 cytokine response. Humanized monoclonal antibodies can be developed against deleterious cytokines, and salutary cytokines can be administered as recombinant molecules. Cytokine manipulations have been most notably successful in the treatment of inflammatory bowel disease.

Finally, gene therapy and gene silencing techniques are also potentially effective strategies. Autoimmune hepatitis is a polygenic disease, and therefore it is not possible to treat the disease through the replacement of a single gene. However, gene therapy may modify different genetic polymorphisms that favor disease severity or progression. In this fashion, it may be possible to manipulate factors that affect cell growth, immunocyte proliferation and survival, hepatocyte regeneration, and collagen deposition.

Gene silencing is a visionary concept in the treatment of autoimmune hepatitis. With gene silencing, small inhibitory RNAs and short hairpin RNAs are synthesized to match sequences in the messenger RNA generated by genes implicated in disease activity. After entering the cell, the small inhibitory RNAs are incorporated into a cytoplasmic silencing complex where they interact with the messenger RNA from the gene of interest. The messenger RNA of the intended gene is then cleaved, and expression of the gene product impaired. Modifications of gene expression in this fashion have already proven useful in inhibiting replication of hepatitis B and C viruses and preventing Fas-mediated apoptosis in an animal model of fulminant hepatitis.

There is a need for new treatments of autoimmune hepatitis, and an obligation for clinical investigators to evaluate the new drugs and molecular interventions that are available for testing. The knowledge, drugs, and technologies already exist to develop site-specific drug and molecular interventions. There has been progress toward more rational therapies, but more effort and help are required. The emergence of a collaborative network of clinical investigators who can perform drug trials quickly and reliably and the characterization of a confident experimental animal model of the human disease are priorities for continued progress.

Suggested Reading

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