ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Current and Emerging Treatments for Autoimmune Hepatitis

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G&H What is the current understanding of autoimmune hepatitis and its pathogenesis?

EW Autoimmune hepatitis (AIH) is a composite of diseases marked by immune dysregulation targeting hepatocytes in the absence of infection. This immune dysregulation leads to inflammation in the liver. Clinically, this is seen as transaminase elevations alone in the nonsevere presentation of AIH. In severe AIH, clinicians often see hepatocellular jaundice, which is elevated bilirubin without cholestatic liver injury (R factor >5).

There are 2 components to the pathogenesis of AIH. One involves genetic predisposition. There are certain human leukocyte antigen alleles that increase the risk that a person can develop an autoimmune disease. However, why a person with 1 of these at-risk alleles develops AIH while their sibling develops, for example, autoimmune thyroid disease is not known. Clinicians see autoimmune diseases run in families, but it is rare to see a family with more than 1 person with AIH. As for the other pathogenetic component, immunologically, AIH is a T-cell–driven disease, which may be surprising because B-cell markers are often used for its evaluation. A histologic feature of AIH is plasma cell infiltrates. Autoantibodies (antinuclear antibodies, smooth muscle antibodies, liver kidney microsomal antibodies, antisoluble liver antigens) are used for disease diagnosis, and immunoglobulin G is used for diagnosis and treatment response. However, these B-cell–related features are driven by aberrant T-cell signaling.

G&H How well do the current treatment strategies for AIH work?

EW The current therapies tend to be broad-based immunosuppressants that impair or inhibit T-cell activation. For decades, the first-line AIH treatment was a systemic corticosteroid plus azathioprine. Corticosteroids, either prednisone or prednisolone, were initiated at the time of diagnosis. Azathioprine was sometimes started simultaneously and other times started several weeks or months later, but the intention was always to taper the corticosteroids to achieve a long-term corticosteroid-free regimen. In the past, patients who were intolerant to azathioprine often had to remain on corticosteroids long term. Mycophenolate mofetil has gained traction over the past 25 years as a second-line agent for patients intolerant to azathioprine.

In 2010, a landmark study demonstrated that budesonide, a corticosteroid with significant first-pass metabolism in the liver, could be used instead of conventional systemic corticosteroids in patients without cirrhosis. Patients receiving budesonide typically experience fewer glucocorticoid-related side effects. However, it is always the goal to eventually be free of any corticosteroid, whether it is budesonide or a conventional systemic corticosteroid.

What are typically used now are corticosteroids with either mycophenolate mofetil or azathioprine, and those regimens tend to be effective in many patients. Data from randomized trials and observational cohorts (both retrospective and prospective) suggest that approximately half of patients achieve complete biochemical response (CBR) 6 months after initiation of therapy. CBR essentially means attaining alanine aminotransferase, aspartate aminotransferase, and immunoglobulin G levels within the upper limits of normal. The concept of CBR has gained traction in the past 5 years or so because patients who achieve CBR have much better clinical outcomes (decreases in hepatic decompensation, liver transplantation, and death). If patients can achieve CBR early, they will do very well. However, if only half of patients are achieving CBR, that means that the other half is in need

of a different or an additional treatment. Fifty percent is not good enough; closer to 100% is the goal in medicine.

G&H What was the last major breakthrough or change in AIH management?

EW If this question had been asked a year ago, the answer would have been the landmark study in 2010. However, in December 2023, results from the CAMARO study were released online, which I consider to be the most recent major breakthrough in AIH. This prospective randomized trial of treatment-naive patients with AIH was the first to compare mycophenolate mofetil to azathioprine head-to-head. Patients who received mycophenolate mofetil were much more likely to achieve CBR at 6 months than those receiving azathioprine (56.4% vs 29.0%, respectively).

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I have used both mycophenolate mofetil and azathioprine frequently in my patients with AIH and have noticed more day-to-day side effects with the use of mycophenolate mofetil than with azathioprine. At the same time, mycophenolate mofetil seems to be much more effective than azathioprine. Therefore, I can see a switch occurring over the next several years and mycophenolate mofetil becoming first-line therapy, although clinicians would likely talk with their patients about associated data and let them decide which agent to try first.

G&H What are the main challenges of developing new drugs and designing clinical trials for AIH?

EW One is that AIH is an orphan disease. A study from 2022 led by my colleague Dr Therese Bittermann looked at the prevalence of AIH diagnoses in the Optum database, a large insurance claims database in the United States. Using her prevalence estimates and the estimated US population of adults, there are approximately 60,000 to 70,000 adults in the United States with a history of AIH. As discussed previously, approximately half of that population will achieve CBR with the current therapies. That means approximately 30,000 to 35,000 adults are not responding to current first- and second-line treatments and need new therapeutic options. That number decreases even further after taking away patients who have decompensated liver disease or who have undergone liver transplantation. It is difficult to obtain a good estimate of that number, but it is likely in the 5,000 to 10,000 range. Thus, the patient population for whom a new AIH drug is needed today could be 20,000 to 30,000 adults.

There are also several challenges created by trial design limitations. The inclusion criteria for AIH trials are very limiting. Patients need to have an AIH activity that is high enough to measure response. If patients have mild disease activity, it may be difficult to see whether there is improvement with the variability typically seen on a surveillance biopsy not able to capture small changes. Additionally, to get into a study, patients need to have elevated transaminases, which makes logical sense because part of the definition of CBR is that transaminases are normal. However, there is a subset of patients with AIH who have normal transaminases, which tends to be patients with cirrhosis; I have had patients with cirrhosis who had normal transaminases and were found to have AIH upon liver biopsy.

The exclusion criteria of AIH trials are very limiting as well. The goal is to exclude any patients who may not be healthy enough to complete the trial. Investigators are looking for patients who have a life span at least past the trial, as well as patients who are unlikely to be hospitalized during the trial for any underlying medical diseases. Investigators also need to make sure patients are not taking medications that may interact with the investigational product being evaluated. Thus, concomitant medications can rule out a patient, as well as a history of cancer, end-stage organ disease, HIV, substance use disorder, arrhythmias, and a second liver disease (including autoimmune overlap of AIH with primary biliary cholangitis or primary sclerosing cholangitis, which can be seen in approximately 10% of patients).

Patient reluctance to enter a trial can also be a challenge. Even after taking into consideration all of the inclusion and exclusion criteria, perhaps the participating trial sites are too far away. Maybe the patient has a full-time job and cannot take time off from work to participate in the trial. Many liver disease trials require a liver biopsy at the beginning of the trial for entrance and then at the end of the trial to see the treatment effect. Some patients are reluctant to undergo a liver biopsy, not to mention two of them, for a study.

There are also other patient concerns. There is often skepticism in general of receiving an investigational product that is not approved by the US Food and Drug

Administration, although that is true for any clinical trial. Similarly, women of childbearing age are particularly skeptical of possible long-term effects of an investigational product to their potential offspring. Patients are also often concerned about receiving a placebo. Thus, considering all of these challenges, the number of patients who may be eligible for and participate in an AIH study is very small.

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G&H Has there been any recent research looking at the use of B-cell–based therapies for patients with AIH?

EW For patients who do not respond to T-cell–based therapies, B-cell–depleting agents have been used and have been successful. Rituximab is the agent that is typically used off-label. A 2019 case series in *JHEP Reports* looked at 22 patients in 3 countries who received rituximab for AIH treatment. The authors did not report CBR but showed that 71% of patients in the case series were free of AIH flares for 2 years after their rituximab infusions.

G&H What clinical trials are currently underway for AIH?

EW The therapeutic trial landscape for AIH is fairly small. Even so, there are several promising candidates to consider.

Ianalumab is a monoclonal antibody that targets the B-cell activating factor receptor. It is currently in development for the treatment of a number of autoimmune diseases, including Sjögren syndrome, systemic lupus erythematosus (SLE), and immune thrombocytopenia, in addition to AIH. Ianalumab gained recognition for having the first large randomized controlled trial in Sjögren syndrome that achieved its primary endpoint (change in EULAR Sjögren Syndrome Disease Activity Index score). Ianalumab is currently being evaluated for the treatment of patients with AIH that was not responsive to standard treatment. The study has completed enrollment, but results have not been released yet (NCT03217422).

Zetomipzomib is an inflammasome inhibitor under investigation for the treatment of autoimmune diseases such as SLE nephritis and dermatomyositis in addition to AIH. Interim results from the MISSION trial demonstrated that 24 weeks of zetomipzomib improved proteinuria in patients with SLE nephritis. Zetomipzomib is currently being studied in a phase 2a trial that is actively enrolling patients for the evaluation of AIH that is not responsive to standard treatment (NCT05569759).

JKB-122 is a Toll-like receptor 4 antagonist being evaluated for inflammatory liver diseases, including AIH and metabolic dysfunction-associated steatohepatitis. A phase 2 study of JKB-122 in patients with AIH that did not respond to standard treatment was completed in 2021 (NCT02556372) and achieved its primary endpoint of alanine aminotransferase reduction. Complete results from this study as well as news on further studies have not been announced yet.

G&H Are there any other priorities of research in this area?

EW In addition to developing new therapies for AIH that does not respond to standard treatment, there is a need to better understand why some patients are not achieving CBR with standard treatment. In some cases, it may be because of undertreatment, that is subtherapeutic doses. In other cases, it may be related to side effects of medications. There is also likely a genetic component as well as a subtype component that may lead to medication response.

Disclosures

Dr Weinberg is a site principal investigator for the PORTOLA study (NCT05569759).

Suggested Reading

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