

A New Approach for Treatment of Hepatitis C in Hepatitis C-Autoimmune Hepatitis Overlap Syndrome

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Chronic hepatitis C virus (HCV) and autoimmune hepatitis (AIH) overlap syndrome is an uncommon but well-documented condition. There are no standard guidelines for treating this complex disease. Generally, interferon is contraindicated in autoimmune diseases.¹ There are a few case reports and case series in which interferon alfa three times per week or pegylated interferon with ribavirin have been used with immunosuppressive medications such as prednisone and azathioprine, with variable response.^{2,3} We report a case of HCV-AIH overlap syndrome that was first treated aggressively with immunosuppressive therapy, with partial response, and subsequently treated with consensus interferon (Infergen; interferon alfacon-1, Three Rivers Pharmaceuticals), achieving sustained virologic response (SVR). To our knowledge, the use of consensus interferon has not been reported in the literature for the treatment of chronic HCV in the presence of AIH.

Case Report

A 40-year-old white woman with a body mass index of 27.1 kg/m² was referred to our medical center for treatment of chronic HCV. Her only complaints consisted of generalized fatigue and joint aches and pain. Her chronic HCV infection was allegedly acquired via blood transfusion in the early 1990s. The patient denied a history of intravenous drug use, tattoos, or high-risk sexual

activity, and her past medical history was only significant for mild depression. No stigmata of advanced liver disease were seen on physical examination. Her initial laboratory data revealed an alanine aminotransferase (ALT) level of 313 U/L (normal, 9–52 U/L), aspartate aminotransferase (AST) of 380 U/L (normal, 14–36 U/L), total bilirubin of 0.4 mg/dL (normal, 0.2–1.3 mg/dL), albumin of 4.6 g/dL (normal, 3.5–5 g/dL), international normalized ratio of 1.1, and HCV RNA viral load of 7,290,000 IU/mL (6.8 logs). Genotype analysis revealed that the patient had HCV genotype 3A, and serologic markers of AIH were positive. Antinuclear antibody (ANA) measured 1:80, antismooth muscle antibody (ASMA) measured 1:160, and immunoglobulin G (IgG) measured 2,369 mg/dL (normal, 694–1,618 mg/dL); thus, AIH type 1 was suspected. Ultrasound of the liver demonstrated fatty liver, and liver biopsy findings revealed chronic hepatitis, with grade 3 necroinflammatory activity with a mixture of plasma cells and portal lymphocytes focally invading the bile ducts. Steatosis with ballooning and steatohepatitis were also noted (Figures 1, 2, and 3). Fibrosis was graded as stage 3. The biopsy findings were consistent with both AIH and chronic HCV, with predominant features of viral hepatitis. Co-infection with hepatitis B and other liver diseases such as hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, and primary biliary cirrhosis were excluded by the appropriate laboratory tests.

The patient was started on oral prednisone 30 mg and azathioprine 50 mg daily. After 4 weeks of therapy, her AST and ALT levels improved to 75 U/L and 125 U/L, respectively. Her azathioprine dose was increased to 100 mg (1.5 mg/kg body weight) daily, and

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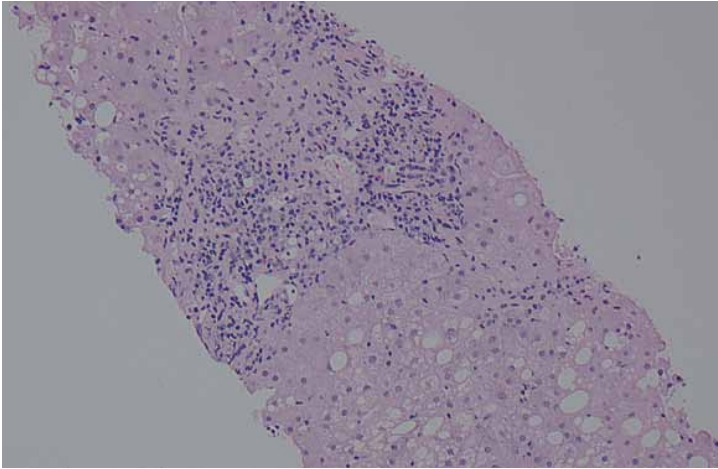


Figure 1. Hematoxylin and eosin stain of liver biopsy revealing steatosis, portal inflammation, and piecemeal necrosis (interface hepatitis). 10× magnification. Image courtesy of Manjula Balasubramanian, MD, FCAP, Chief of Clinical Pathology and Laboratory Medicine, Albert Einstein Healthcare Network, Philadelphia, Pennsylvania.

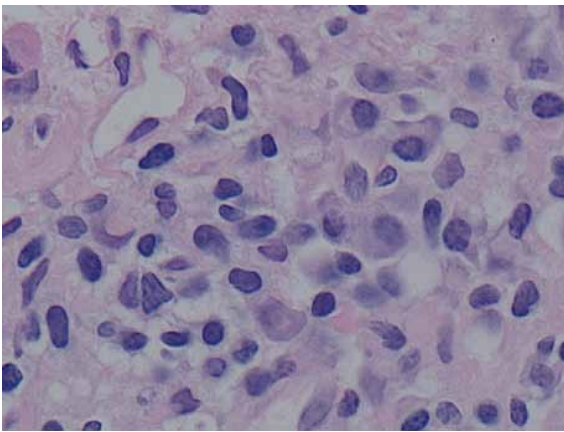


Figure 2. Hematoxylin and eosin stain of liver biopsy revealing plasma cells and lymphocytes invading bile ducts. 60× magnification. Image courtesy of Manjula Balasubramanian, MD, FCAP, Chief of Clinical Pathology and Laboratory Medicine, Albert Einstein Healthcare Network, Philadelphia, Pennsylvania.

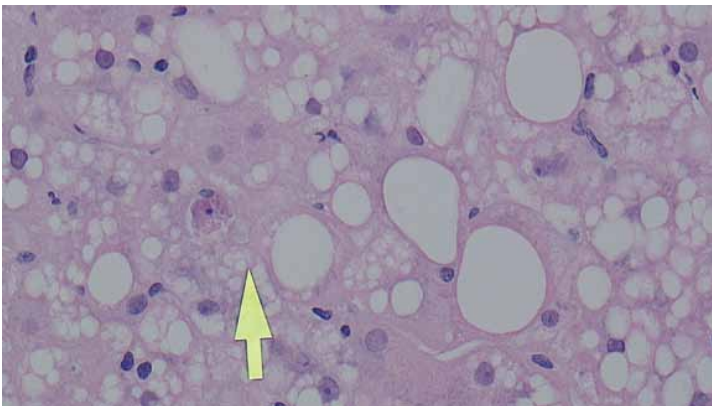


Figure 3. Hematoxylin and eosin stain of liver biopsy revealing steatosis, balloon cells, and apoptosis (arrow). 40× magnification. Image courtesy of Manjula Balasubramanian, MD, FCAP, Chief of Clinical Pathology and Laboratory Medicine, Albert Einstein Healthcare Network, Philadelphia, Pennsylvania.

her prednisone dose was decreased to 25 mg daily. The patient was monitored for the next 3 months on the same regimen, without any further improvement in transaminase levels. Due to the suboptimal response to first-line therapy, alternative treatment with oral prednisone

25 mg and mycophenolate mofetil (Cellcept, Roche Palo) 500 mg twice daily was started. The mycophenolate mofetil was gradually increased to 1 g twice daily (total, 2 g daily). This regimen was continued for the next 4 months, but no improvement in transaminase

levels was observed. The prednisone was tapered and then discontinued over a 1-month period while the mycophenolate mofetil was continued. The AST and ALT levels remained elevated at 99 U/L and 115 U/L, respectively.

As a result of the suboptimal response to prednisone and mycophenolate mofetil, treatment for HCV was started. The risks and benefits were discussed with the patient in great detail, including the possibility of AIH flare-ups while on interferon. At the start of treatment, the patient's viral load was 9,650,000 IU/mL. After clearance from the ophthalmology and psychiatry departments (the latter of which started the patient on a stable dose of oral duloxetine [Cymbalta, Eli Lilly]), consensus interferon 15 µg three times per week, subcutaneously, with ribavirin 800 mg/day orally were started. As treatment was well tolerated without any significant side effects, consensus interferon was increased to a daily dose after 4 weeks. The patient responded very well to the therapy and achieved rapid virologic response (defined as an undetectable viral load at Week 4 of treatment), with normalization of liver transaminase levels. The patient successfully completed 24 weeks of treatment with consensus interferon and achieved end-of-treatment response (defined as an undetectable viral load at the completion of treatment) and SVR (defined as an undetectable viral load after 24 weeks following completion of treatment). The patient also took growth factors such as filgrastim (Neupogen, Amgen) and epoetin alfa (Procrit, Amgen). Although mycophenolate mofetil was continued throughout the interferon treatment without any evidence of AIH flare-ups, secondary to neutropenia, the dose of mycophenolate mofetil was decreased from 2 g/day to 1.5 g/day. After the successful completion of consensus interferon therapy, the mycophenolate mofetil dose was gradually decreased over 6 months to 750 mg/day.

Discussion

There are 3 types of AIH.⁴ Type 1, which our patient had, is seen more frequently in middle-aged to elderly women, has higher levels of IgG, shows a better response to steroid therapy, and progresses less frequently to cirrhosis compared to the other types.⁴ The concurrent presence of AIH in chronic HCV-infected patients constitutes HCV-AIH overlap syndrome. These patients manifest clinical, histologic, biochemical, and immunologic features of both HCV and AIH. Serologic markers of AIH such as ANA (10–33%), ASMA (13–66%), or anti-liver and kidney microsomal (LKM) antibody-1 (0–3%) have been reported in chronic HCV-infected patients.^{5–7}

This concurrence of viral infection and autoantibodies not only confounds the diagnosis but also complicates the treatment strategy. Generally, interferon is contraindicated in autoimmune diseases. Almost all patients treated with pegylated interferon and ribavirin experience 1 or more adverse events during the course of therapy. The most common of these adverse events are influenza-like symptoms, psychiatric symptoms (depression, suicidal thoughts, irritability, and insomnia), and bone marrow suppression. Less common adverse events include weight loss, hair loss, thyroid dysfunction, pulmonary toxicity, colitis, vision loss, and hypersensitivity reaction.^{1,8} Administration of interferon in patients with chronic HCV-AIH overlap syndrome can lead to an exacerbation of the underlying AIH.^{9,10} This situation is well described by papers such as those by Vento and associates and Papo and colleagues.^{11,12} Treatment with immunosuppressive therapy rarely leads to complete normalization of liver biochemical profile and is frequently accompanied by an increase in HCV RNA level.¹³

To date, there are no standard guidelines on how to approach patients with HCV-AIH overlap syndrome. One management strategy is to determine the predominant entity in order to select the appropriate type of therapy.^{2,14} Chronic HCV-AIH overlap syndrome can be divided into autoimmune- or viral-predominant disease. Patients with autoimmune-predominant disease have ASMA or ANA titers of equal to or more than 1:320 or have ASMA and ANA titers of equal to or more than 1:40, as well as histology findings that include piecemeal necrosis (interface hepatitis), lobular hepatitis, and portal plasma cell infiltrates.^{14–16}

Patients with viral-predominant disease have ASMA or ANA titers of less than 1:320 or have antibodies to LKM type-1 and hepatitis C viremia, as well as histology findings that include portal lymphoid aggregates, steatosis, or bile duct injury. Tissue damage is more focal in HCV and more diffuse in AIH liver histology.^{14–16} An immunosuppression trial with corticosteroids (CS) monotherapy or reduced-dose CS combined with azathioprine is an option for patients with autoimmune-predominant disease. Cyclosporine may be effective as short-term front-line therapy, and calcineurin inhibitors may salvage patients who are refractory to CS regimens.^{2,14,17,18} Interferon therapy with close monitoring is an option in viral-predominant disease.¹⁴

Conclusion

We present a case of HCV-AIH overlap syndrome. Due to the discordant treatment options of HCV and AIH, it is challenging to determine therapy when the diseases

coexist. In our case, consensus interferon was preferred due to its strong potency and short half-life¹⁹ compared to pegylated interferon and natural interferon alfa. If the patient had developed a flare of AIH, treatment would have been stopped and rapid washout of the system could have been achieved. We realize that our patient had a very favorable genotype (genotype 3A), which responds better to treatment than genotype 1 and has a very high response rate to interferon. However, we suggest that this approach can be attempted in selected patients with other genotypes as well, under close observation and with regular follow-ups, particularly with a hepatologist. For the future, however, further studies and larger case series are required to establish appropriate guidelines.

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Review

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Hepatitis C virus–autoimmune hepatitis (HCV-AIH) overlap syndrome has been described in the literature since the early 1990s with numerous case reports and proposed guidelines of management.¹⁻⁵ However, definitive diagnosis and appropriate therapy for the syndrome remain controversial and there are still no formalized

treatment strategies. Azhar and associates describe the case of a 40-year-old woman with HCV-AIH who was treated initially with steroids and immunosuppression and subsequently with consensus interferon (Infergen; interferon alfacon-1, Three Rivers Pharmaceuticals) and ribavirin with success.⁶ This case raises a number of important and interesting points concerning the diagnosis, management, and potential pitfalls of treatment.

The diagnosis of true HCV-AIH is often challenging, as the concurrent presence of serologic markers typically found in AIH and serologic evidence of HCV infection is well documented.^{7,8} EIA-3, the third-generation enzyme-linked immunosorbent assay anti-HCV screening test, which is currently used in many institutions, appears to have increased sensitivity in the high-prevalence setting⁹ and more than 99% specificity in the blood donor population.¹⁰ However, autoantibodies such as anti-nuclear antibody (ANA), antismooth muscle antibody, or anti-liver and kidney microsomal 1 antibody have been reported in 9–38%, 5–91%, and 0–10%, respectively, of patients with chronic HCV infection.⁴ Therefore, in order

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to definitively diagnose HCV-AIH overlap syndrome as a distinct entity, the existence of both diseases must be confirmed independently. The diagnosis of HCV is relatively straightforward, as evidenced by positive antibody +/- viremia, though a modest proportion (up to 19%) of patients with AIH do demonstrate HCV RNA in their serum.⁵ The International Autoimmune Hepatitis Group (IAIHG) has defined 3 categories for diagnosing AIH: not AIH, probable AIH, and definite AIH.¹¹ Prospective validation of these cohorts has suggested a sensitivity of 97–100% for the diagnosis of AIH.^{12,13} These criteria were subsequently revised in 1999.¹⁴ More recently,¹⁵ the IAIHG has streamlined the diagnostic criteria, with a sharper focus on the clinical diagnosis of AIH, with the aim of making the criteria more readily usable. According to the 1999 criteria, the patient reported by Azhar and colleagues at most meets criteria for probable AIH, as positive viral markers and biliary changes on histology decrease the overall score significantly. According to the simplified criteria, using the patient's provided laboratory values yields an overall score of 5, whereas a score of 6 or greater is required to make a diagnosis of probable AIH. Furthermore, as it has been pointed out,¹⁶ and as evidenced by the scoring systems, a higher titer of ANA confers a higher likelihood of definite AIH. In this case, the ANA titer, though positive, was only 1:80 in the presence of HCV and thus not typical of true HCV-AIH overlap syndrome.

Histologic diagnosis of the overlap syndrome is another important consideration. Although no single histologic feature is pathognomonic of either HCV or AIH, distinct composite histologic patterns have been described for each entity. In general, patients with AIH are more likely to have severe lobular necrosis and inflammation, piecemeal necrosis, multinucleated hepatocytes, and broad areas of parenchymal collapse, whereas patients with HCV are more likely to have bile duct damage, bile duct loss, steatosis, and lymphoid cell follicles within portal tracts. The combination of portal lymphoid aggregates and steatosis was found to have 91% specificity for HCV, whereas the pattern of lymphoplasmacytic portal, interface, and acinar hepatitis had 81% specificity for AIH.¹⁷ The most common histologic pattern in liver biopsies of patients with HCV-AIH overlap syndrome is consistent with AIH, though the HCV pattern and a mixture of both AIH and HCV patterns can also be present. In addition, the AIH histologic pattern is associated with higher serum levels of γ -globulins and a higher frequency of cirrhosis, compared to the HCV pattern.¹⁸ In the current case, although necroinflammatory changes are more consistent with AIH, they can also be seen in HCV; bile duct damage and steatohepatitis together significantly favor a diagnosis of HCV. Thus, the biopsy is more suggestive of HCV with autoimmune features.

Another important consideration is the type of treatment once a diagnosis of HCV-AIH overlap syndrome is made. The discordant forms of treatment for HCV infection and AIH have made medical management of this overlap syndrome difficult. Administration of interferon to patients with HCV infection complicated by autoimmune features has led to an exacerbation of the underlying AIH.^{19,20} In fact, it has been recently shown that a *de novo* type of AIH can develop after liver transplantation secondary to interferon treatment for HCV.^{21,22} In contrast, an improvement of serum aminotransferase levels in patients with chronic HCV infection has been observed with corticosteroid administration; however, complete normalization of liver chemistry tests (LCT) rarely occurs in these patients.²³ In addition, these biochemical improvements are frequently accompanied by increased levels of viremia.²⁴ As noted by the authors, according to most experts, the approach to the management of patients with HCV-AIH overlap syndrome must start with the determination of the predominant entity to allow for the selection of the most appropriate form of therapy.²⁵ In cases where one disease does not appear to predominate, a possible approach may be to target the more treatable disease first, such as HCV genotype 2 or 3.

Given these general considerations, there are a number of important management questions that pertain to this case. Due to the potential challenges and concerns that treatment of one disease could exacerbate the other, clinicians may be reluctant to commence any treatment at all and employ a watch-and-wait approach. In our experience, and as demonstrated by this case, the long-term benefits of treatment usually outweigh the risks. As noted above, the most pressing question is often which entity to tackle first. In this case, given the apparent predominance of HCV, as well as the favorable genotype, the use of interferon initially may have been more prudent. Another question is the choice of treatment for the AIH component. The authors initially used prednisone and azathioprine and then changed to mycophenolate mofetil (Cellcept, Roche Palo) due to a suboptimal response. Patients with true AIH demonstrate a rather rapid response to steroid treatment; therefore, the lack of complete response after 4 months of treatment may have been an indication that the HCV component was the main contributor to the persistently elevated LCT. Additionally, although the investigators increased the dose of azathioprine to 1.5 mg/kg/day, the literature appears to support maximizing the dose of azathioprine in nonresponsive patients to 2 mg/kg/day.³ Furthermore, although mycophenolate mofetil is now well-accepted as second-line treatment for AIH, much data indicate that it is not more efficacious for patients who do not respond to first-line therapy and should mainly be reserved for those who are unable to tolerate the side effects of azathioprine.²⁶

Finally, clinicians should be aware that azathioprine itself can cause an increase in LCT during therapy.

Another important consideration is when to discontinue treatment of one disease entity and when to consider treating the other. The authors continued treatment of AIH for approximately 9 months prior to starting the HCV treatment because of an insufficient biochemical response. One may argue that, when possible, a second liver biopsy should be performed to gauge any interval disease change after therapy. Furthermore, a biopsy may elucidate whether the patient should be converted to the second form of treatment completely or whether the initial therapy should be continued in some form, as the authors chose to do with mycophenolate mofetil. This is particularly important given the considerable hematologic side-effect profile of this medication, which may further complicate HCV treatment. We agree with the choice of consensus interferon, rather than the pegylated form, given the concern for possible flares of AIH during HCV treatment and to allow better control of the side effects of the interferon. In addition, there are emerging data showing that pegylated interferon itself may induce autoimmune antibodies and other phenomena.^{27,28}

Despite many case reports and much data on the overlap of HCV and AIH, this syndrome remains poorly elucidated. Although there are some recommendations in the literature, methods to secure a definitive diagnosis and treatment strategy continue to be controversial. Recent trends indicate that the best approach may be to determine the more predominant and easily treated entity and then to employ sequential therapy based upon this information. Nevertheless, these decisions remain extremely challenging, and clinicians must use their clinical knowledge and cautiously treat each patient on an individual basis. We applaud the investigators for their success, though we may have made slightly different choices. However, it is clear that, in most cases, offering treatment of one disease, using the above approach, though riddled with anxiety, will likely be beneficial to the patient.

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