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EDITORIAL

Optimizing management in autoimmune hepatitis with liver failure at initial presentation

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Abstract

Autoimmune hepatitis (AIH) is a disease of unknown HWLRORJ\ WKDW PDLQO\ DIIHFWV ZRPHQ DQG KDV D ÀXFWXDWLQJ SUHVHQWD-tion. By its very nature, it is a chronic condition, although increasingly, we are becoming aware of patients with acute presentations, some of whom may have liver failure. There are very limited published data on patients with AIH with liver failure at initial diagnosis, which consist mostly of small retrospective studies. As a consequence, the clinical features and optimal management of this cohort remain poorly defined. DJHPHQW RI WKLV FRKRUW UHPDLQ SRRUO\ GHÀQHG. $ VXEVHW of patients with AIH who present with liver failure do respond to corticosteroids, but for the vast majority, an urgent liver transplantation may offer the only hope of long-term survival. At present, there is uncertainty on how best to stratify such a cohort into responders and non- responders to corticosteroids as soon as possible after hospitalization, thus optimizing their management. This editorial attempts to answer some of the unresolved issues relating to management of patients with AIH with liver failure at initial presentation. However, it must be emphasized that, at present, this editorial is based mostly on small retrospective studies, and it is an understatement that multicenter prospective studies are urgently needed to address this important clinical issue.

Key words: Autoimmune hepatitis; Liver failure; Liver transplantation; Corticosteroids

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INTRODUCTION

Autoimmune hepatitis (AIH) is a disease that is characterized by chronic hepatic inflammation, presence of autoantibodies [antinuclear antibody (ANA), anti-smooth muscle antibody (SMA), and liver kidney microsomal (LKM) antibody], female preponderance and elevated serum gammaglobulins, especially IgG[1]. Earlier studies have established the beneficial effects of corticosteroids in AIH and up to 80% of patients can now achieve remission with immunosuppressants[2,3]. At accession, 10%-20% of patients with AIH can be negative for the conventional autoantibodies[4], although their outcomes, especially response to immunosuppression, are no different from those that are autoantibody-positive[5].

AIH can have protean manifestations, with the majority of patients presenting with subclinical or chronic disease. However, in > 25%, the disease may present acutely with jaundice, a subset of whom may have fulminant or subacute liver failure (LF)[6-8]. Fulminant hepatic failure (FHF) is a devastating clinical condition that occurs in patients

Table 1 Clinical characteristics of patients with autoimmune hepatitis with liver failure at initial presentation

	Villamil *et al*[22][1] (*n* = 28)	Kessler *et al*[23] (*n* = 10)	Miyake *et al*[24] (*n* = 11)	Ichai *et al*[25] (*n* = 16)	Verma *et al*[7] (*n* = 20)
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Age (yr)[2]	41	40 ± 15.9	53 (16-75)	36 ± 13.1	41.3 ± 14.2
Definition of LF	NA	NA	PT < 40% and HE ⩾ grade 2	HE within 12 wk of jaundice	Any grade HE and/or INR > 2
Symptoms duration[2]	NA	3.2 wk	24 (16-52) d	NA	2.1 ± 2.5 mo[3]
Female	NA	8 (80%)	11 (100%)	14/16 (87.5%)	15 (75%)
Ethnicity or country of origin	South American	80% White	Japanese	French	70% black
Definite/probable AIH (IAIHG[4] criteria)	NA	NA[5]	3(36%)/8 (64%)	NA	9(45%)/11(55%)
LC/LKM[6] positive	6 (21.4)	1 (10%)		3 (18.7%)	NA
ANA/SMA[7] positive	22 (78.5%)	7 (70%)	NA	11 (68.7%)	20 (100%)
Bilirubin[2] (mg/dL)	398[8]	16.97 ± 9.83	20.6 (5.9-31)	425 (278-850)[8]	19.3 ± 10.3
AST or ALT[2]	NA	1179 ± 1127.17	220 (59-1094)	678 (60-2867)	1147.1 ± 711.4
INR[2] or PT	30%	49.3 ± 66.9	29% (6%-38%)	5.36 (1.7-12.2)	2.7 ± 1.4
HE[9] at onset	28 (100%)	8 (80%)	11 (100%)	10 (62.5%)	19 (95%)
Cirrhosis	None	2/10 (20%)	NA	None	8/20 (40%)
MELD[2]	NA	NA	NA	37 (24-47)	28 ± 7.41
Sub-massive or massive necrosis (SMN, MN)	19/23 (82.6%) 17 needed LT and/or died	5/10 (50%)	NA	16/16 (100%) 15 needed LT and/or died	12/19 (63.1%), 10 needed LT and or died
Immunosuppressant regimen used	Prednisone 60 mg/d	Corticosteroids (Dose NA) and other[10]	Prednisolone 40-60 mg/d and steroid pulse	Prednisone 1 mg/kg per day and other[10]	Corticosteroids[11] 20-1250 mg/d
Poor prognostic criteria	1: PT < 20%; 2: Grade 4 HE; 3: SMN at diagnosis; 4: 20% increase in PT at day 3 of steroids	NA	1: High bilirubin at onset; 2: Worsening bilirubin during days 8-15 of steroid therapy	NA	1: Absence of cirrhosis; 2: MELD > 28; 3: Worsening trend in bilirubin and INR after 3.7 ± 0.6 d of steroid therapy
Septic events	NA	NA	NA	7 (43.7%), of whom 6 had received steroids	2 (10%), of whom 1 received steroids

[1]Published only in abstract form; [2]Data presented as mean ± SD or median (range); [3]Duration from first symptom (and not necessarily jaundice/hepatic encephalopathy) to hospitalization; [4]IAIHG: International Autoimmune Hepatitis Group; [5]Met IAIHG criteria, data on probable or definite disease unavailable; [6]LKM/LC: Liver kidney microsomal antibody/liver cytosol antibody; [7]ANA/SMA: antinuclear antibody/anti-smooth muscle antibody; [8]Values in μmol/L; [9]HE: Hepatic encephalopathy; [10]Additional immunosuppression was used in nine patients in the study of Kessler *et al* (azathioprine, tacrolimus, mycophenolate mofetil, 6-mercaptopurine, cyclosporine) and in one patient in the study of Ichai *et al* (azathioprine and cyclosporine); [11]Included prednisone, hydrocortisone and methylprednisone, (converted to equivalent doses of prednisone); LT:Liver transplantation; PT: Prothrombin time; AIH: Autoimmune hepatitis.

therapy survived, obviating the need for a subsequent LT. Unfortunately, among the non-responders to corticosteroids in these five studies (*n* = 46), death was the inevitable outcome in the absence of LT (Table 2). The duration of steroid therapy prior to death was highly variable (3-95 d). Clearly, in some, the illness was so fulminant that death occurred rapidly after hospitalization, thereby precluding LT, and in others, there were active contraindications to transplantation, such as sepsis (Table 2). Nevertheless, in these five studies, there were a subset of patients with AIH and LF in whom death may have been preventable had LT been more aggressively pursued. It is conceivable that initiation of steroids provided a false sense of security, thereby delaying transplant evaluation.

One could argue that the low remission rates to corticosteroids in this cohort were partly related to delay in initiating therapy. However, where available, the data do not support this conclusion, as corticosteroids were initiated promptly, especially in the sicker patients. In our study, subsequent non-responders to corticosteroids were commenced on therapy within 2.6 ± 1.8 d of admission, compared to 6.4 ± 5.5 d in those who eventually responded to corticosteroids[7]. It is more likely that non-responders to corticosteroids had aggressive disease at the time of diagnosis with a critical degree of liver cell death already having occurred prior to the introduction of medical treatment[24]. This hypothesis is supported by the study of Ichai *et al*[25], in which all patients had massive/sub-massive liver necrosis (median MELD score at admission: 37), with only 8.3% responding to corticosteroids and > 80% needing LT.

OPTIMIZING MANAGEMENT IN PATIENTS WITH AIH AND LF

Assessing patients with LF for LT is a complex process. The most widely used criteria for prioritizing patients for LT are the King's College criteria[30]. However, neither the King's College criteria[29] nor the more recently developed MELD score[31] have been validated in patients with AIH and LF. This is most likely due to the fact that the prevalence of AIH in patients with LF being evaluated for LT is low (0%-5%)[12,13,32]. As is evident from the published data[7,22-25], there certainly are a subset of patients with AIH and LF who will respond to corticosteroids. Inappropri-

Table 2 Outcomes of patients with autoimmune hepatitis and initial presentation with liver failure

ate transplantation in such patients would mean subjecting them to unnecessary surgery (and its attendant complications) and lifelong immunosuppression. In addition, it would deprive another more suitable recipient from receiving the graft[33]. On the other hand, denying LT to a patient with AIH and LF who is unlikely to respond to corticosteroids means condemning them to a certain death, which is unacceptable, especially since post-transplant survival for AIH is excellent [estimated 5-year survival probability after first LT is 0.73 (95% CI: 0.67-0.77)][34].

The contentious issue thus is how best to stratify patients with AIH and LF into likely responders and non-responders to corticosteroids as soon as possible after hospitalization; hence optimizing their management. In our study[7], all responders to corticosteroid therapy had a MELD score ≤ 28 at admission. This is also supported by Ichai *et al*[25], who showed that the only patient to respond to corticosteroids had a MELD score of 24, and none with an initial MELD score > 28 responded to corticosteroids. Furthermore, in our study, responders to corticosteroids were more likely to have either an improvement or stabilization in bilirubin and INR within 3.7 ± 0.6 d of initiation of corticosteroid therapy, whereas non-responders tended to have a trend for higher bilirubin and INR[7]. Villamil *et al*[22] also observed that a 20% increase in prothrombin time (PT) at day 3 of corticosteroid therapy to be a predictor of poor outcome, along with PT < 20% , grade 4 encephalopathy, and LKM antibody/liver cytosol (LC) antibody positivity at diagnosis. Histological evidence of sub-massive/massive necrosis is also invariably associated with need for LT and/or death (Table 1). Surprisingly, in our study, the presence of cirrhosis was more likely was associated with response to corticosteroids[7]. Although the impact of cirrhosis on the natural history of AIH remains controversial[27,28,35,36], it is likely that this group has long-standing indolent disease that progresses to cirrhosis, with LF representing an acute relapse of AIH[37]. This is in contrast with the study of Ichai *et al*[25], in which absence of significant hepatic fibrosis in all the patients indicated a *de novo* fulminant disease process.

CORTICOSTEROIDS AND INFECTIONS

Whether steroids increase the risk of septic complications in patients with severe liver disease is subject to an ongoing debate. The issue becomes even more contentious in the presence of LF because in itself that has been associated with an increased risk of bacterial and fungal infections[25,38,39]. In fact, earlier studies have shown that up to 35% of patients with LF can develop bacteremia in the pre-transplant period[39]. This increased propensity for sepsis is further aggravated in the post-transplant setting due to use of immunosuppression. Therefore, not surprisingly, sepsis with or without multiorgan failure, accounts for almost one-third of all deaths in patients undergoing LT for LF, and is the most common cause of mortality in this cohort[40]. In the study of Ichai *et al*[25] (which had the sickest cohort of patients with a median MELD score of 37 at admission), 42.3% developed a septic event, and this prevalence is not higher than that reported previously[39]. It is however noteworthy that in Ichai *et al*'s study septic events were more likely to occur in those initiated (6/12) versus those not initiated (1/4) on corticosteroids[25]. It is unclear whether patients received prophylactic antibiotics in this study. Reich *et al*[41] also have reported an increased trend for wound infection in corticosteroid-treated patients with AIH undergoing LT (30.7% *vs* 5.2%). In a recent publication that analyzed data from the European Transplant Registry, in comparison with transplantation for primary biliary cirrhosis and alcoholic cirrhosis, the probability of infectious complications limiting patient survival was significantly increased after transplantation for AIH. This was especially relevant to patients aged > 50 years and within the first 3 mo of transplantation[34]. Unfortunately, data on disease severity and use of pre-transplant immunosuppression and prophylactic antibiotics were not available in that study. On the other hand, others have reported corticosteroids not to be associated with increased risk of infections in patients with severe AIH[42]. These discordant results most likely reflect the heterogeneous patient groups (including the whole spectrum from chronic disease to FHF), use of varying immunosuppressive regimens, and inconsistent use of prophylactic antibiotics. Nonetheless, Ichai *et al*[25] caution against injudicious use of corticosteroids in patients with AIH and LF, and on the contrary, emphasize the need for expedited LT evaluation in such a cohort. Furthermore, it lends credence to the argument for the use of prophylactic antibiotics and antifungal agents, because such a strategy has been shown to reduce the risk of infections in the pre-transplant setting[43].

THE FUTURE

Prospective multicenter studies are clearly needed to address this complex and important clinical issue. In future, testing for additional autoantibodies and HLA typing might also help risk-stratify patients. For example, presence of antibodies to SLA have been associated with DRB1 *0301, and such patients have aggressive disease and are more likely to require LT and/or die[44,45].

CONCLUSION

The diagnosis and management of patients with AIH with AF at initial diagnosis can be challenging. Although there are only limited published data available, mostly in the form of small retrospective studies, up to 8.7%-19.8% of patients with AIH may have this form of presentation. On the whole, about one-third can respond to corticosteroids and have a good outcome, although for the vast majority, LT may offer the only hope of long-term survival. A MELD score at admission of $\leqslant$ 28, more severe hepatic fibrosis, absence of sub-massive/massive necrosis, and early (within 4 d) improvement or stabilization in bilirubin and INR, identify those who are likely to respond to

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