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Clinical Studies

Autoimmune hepatitis type 1: safety and efficacy of prolonged medical therapy

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Abstract: Studies on the long-term outcome of immunosuppression in patients with autoimmune hepatitis (AIH) type 1 are limited. *Aim:* To assess the efficacy and safety of prolonged medical therapy for up to four decades in a cohort of patients with AIH. *Methods:* Forty-two patients were followed long term in the Yale Liver Clinics who met the criteria of 'definite autoimmune hepatitis' as defined by the International Autoimmune Hepatitis Group. Records were reviewed for the dosage of immunosuppression, rate of relapse, steroid side effects, current status of liver function tests and evidence for cirrhosis and its complications. *Results:* Mean follow-up was 16 years and ranged from 7 to 43 years. The median follow-up was 13.5 years. Steroid withdrawal resulted in a mean of 1.78 relapses/patient (range, 0–8). All but six patients responded well to prednisone and azathioprine and alanine aminotransferases were completely normal in 29 (81%) at last exam. Five patients have discontinued medication. Steroid side effects have been minimal (weight gain in eight, osteoporosis in three) except for one patient who recovered successfully from cryptococcal meningitis and another with aseptic necrosis of the hip. Progression to cirrhosis occurred in 54% with evidence of esophageal varices in 37% but none developed hepatocellular carcinoma. Only one patient has received a liver transplant, while five others are currently listed because of symptoms of ascites, encephalopathy or bleeding from esophageal varices. *Conclusions:* AIH can be managed effectively over three to four decades with low-dose immunosuppression resulting in essentially normal lifestyles and minimal side effects. Liver transplantation with an increased risk of rejection and graft failure in this group can be avoided for long periods in most of these patients.

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The natural history and long term prognosis of patients with autoimmune hepatitis (AIH) has been greatly altered by immunosuppression regimens and liver transplantation. Early studies of natural history of AIH indicated that mortality was ~90% by 10 years without treatment (1–4). Survival increases dramatically when steroid therapy is initiated (1–4) and 10-year survivals that are similar to age- and sex-matched controls from the population at large are now expected (5, 6). Patients with AIH respond to immunosuppressive agents whether or not cirrhosis is present and long-term medical therapy for more than 20 years is not unusual (5, 7). However, once complications of cirrhosis develop, liver transplantation is recommended for many patients with AIH. Thus data on the effects of long-term medical follow-up are limited.

While liver transplantation has resulted in extended life spans for many patients with chronic liver diseases, mortality from the procedure is not insignificant and most patients require lifelong immunosuppression. Disease reoccurrence and graft rejection may occur. Indeed, it is now becoming apparent that recurrence of AIH following liver transplantation may be significantly higher than most other chronic liver disorders, although criteria for disease recurrence and outcome vary (8–23).

In a recent study, 41% of patients transplanted for AIH, and followed for more than 10 years, developed recurrent disease (24). Such observations suggest that decisions to refer patients with

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AIH for transplant need to be carefully balanced by knowledge of the success or failure of long-term medical therapy in this disease. We therefore reviewed our personal experience with long-term medical treatment in a cohort of patients with AIH type 1 followed for more than 7 and up to 43 years. Our findings indicate that the majority of these patients can be maintained on low dose immunosuppression for many years without disease progression and that with careful management, side effects can be minimized.

Methods

The records of all patients with diagnosis of AIH/cirrhosis who were followed primarily by one of us (J. L. B) in the Liver Clinic at Yale School of Medicine were reviewed. Forty-two patients were identified who fulfilled the following diagnostic criteria: 1) A diagnosis of definite AIH type 1 as defined by the International Autoimmune Hepatitis Group (score of 16–18) (25). 2) Follow-up data were available for all patients within the last 6 months of data collection in 2003. 3) All patients were included in the analysis if they had been followed for at least 7 years.

Data were recorded with respect to age, gender, initial serum markers, and liver function tests, history of drug ingestion or reactions and alcohol intake. Clinical signs of advanced liver disease were recorded, including palmar erythema, spider angiomata, jaundice, ascites, edema, hepatosplenomegaly, and encephalopathy. Serum and biochemical markers included liver function tests (alanine aminotransferase, aspartate aminotransferase, total and direct reacting bilirubin, serum albumin, anti-nuclear antibodies, smooth muscle antibodies, liver–kidney muscle antibodies, serum immunoglobulins, viral hepatitis serologies). Evidence of portal hypertension was noted if esophageal varices were detected or radionucleotide liver spleen scans demonstrated moderate or severe evidence of colloid shift to the spleen and/or bone marrow. Additional data included evidence of other associated autoimmune diseases and whether or not patients had been referred for liver transplantation. The duration and type of immunosuppressive therapy was noted as well as the number of times that biochemical and/or clinical relapses occurred as defined by recurrence of symptoms (e.g. anorexia, nausea, fatigue, abdominal pain), and/or exacerbations in liver function tests. Patients with co-existing viral, drug or alcohol-induced hepatitis were excluded. During the follow-up period, particular attention was paid to findings suggesting disease progression and evolution to cirrhosis. These included abnormal liver spleen scans, the presence of varices demonstrated by either barium X-rays or endoscopy, and follow-up liver biopsies, when available. Complications of steroid therapy were recorded and bone scan results were assessed. Forty-two patients were identified that fulfilled the described criteria for prolonged follow-up of AIH type 1. The mean duration of follow-up was 16 years with a median of 13.5 years and ranged from 7 to 43 years. Table 1 illustrates the major clinical characteristics of this group of patients. Thirty-two of the 42 patients were women. At the time of diagnosis, their mean age was 36.5 and ranged from 13 to 77 years. At the time of inclusion in this study their mean age was 47 and ranged from 24 to 93 years. Original biochemical, serologic, clinical and histological features led to a definitive diagnosis of chronic AIH type 1 as defined by the International Autoimmune Hepatitis Group in all 42 cases. Most patients were jaundiced and clinically decompensated when first seen (Table 2). Liver biopsies were able to be obtained in only 14 patients

Table 1. Cohort characteristics

No. of patients	42
Sex ratio (F/M)	32/10
Age (years), mean (range)	47 (24–93)
No. of patients with definite/probable AIH	42/0
Duration of follow-up (years) mean/range	16 (7–43)
Number of patients follow-up (years)	
>40	1
30–39	7
20–29	8
10–19	14
7–9	12
Associated autoimmune conditions	7
Relapses (mean/range)	1.78 (0–8)
Patients treated with prednisone only	6
Patients treated with imuran only	3
Patients treated with prednisone and imuran	28
Patients referred for liver transplantation	6
Patients off medications	5

F, female; M, male.

Table 2. Liver function tests at study entry

	Mean ± SD	Range	Median
AST			
Normal 0–40 IU/l	802 ± 795	34–2840	690
ALT			
Normal 0–40 IU/l	601 ± 648	53–2890	909
Alkaline phosphatase			
Normal 0–120 IU/l	117 ± 51	24–228	121
Total bilirubin			
Normal 0.3–1.3 mg%	8 ± 8	0.3–35	9.3
Albumin			
Normal 3.2–4.8 g%	3.8 ± 4.0	2.8–4.3	3.5

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

before the initiation of therapy, five of whom already had cirrhosis.

Treatment regimen

Therapy was individualized for each patient. Our general practice was to initiate prednisone therapy at a dose of 30 mg/day. A few patients were treated initially with higher or lower doses that ranged from 7.5 to 50 mg/day depending on the severity of the disease, but the mean starting dose was 29 ± 14 mg/day. Thereafter prednisone was titrated over 2–3 weeks to 20 mg/day when azathioprine was added at 50 mg/day. Prednisone was then slowly tapered in 2.5 mg decrements over a subsequent 4–8 week interval to levels of 10 mg of prednisone together with 50 mg of azathioprine/day. Liver function tests were obtained every 2 weeks during this period. Once aminotransferases (which were used as the primary indicator of response to treatment) fell into the full normal range, the dose of prednisone was further reduced in 2.5 mg increments every 2–3 weeks until patients were receiving 2.5 mg daily. Then 2.5 mg was administered every other day for 4 weeks and then discontinued while azathioprine was continued alone usually for at least several months. If during the steroid taper, the level of aminotransferase either did not decline or increased again (increases in enzymes during therapy are defined as a recrudescence), then either the dose of prednisone was increased by 5–10 mg/day or azathioprine was increased to 75 mg/day, if side effects of the prednisone (irritability, cushingoid facies) were apparent. The steroid taper was begun again once the enzyme levels returned to normal.

Once liver function had normalized and medication was discontinued, follow-up tests of liver function were routinely obtained at 3–6 month intervals in the absence of clinical symptoms. Neither liver biopsies, serum globulin levels or antinuclear antibodies were used as markers of ongoing activity of the disease once serum aminotransferase levels were within normal range. *Relapses* (defined as an increase in the aminotransferase levels with or without recurrence of symptoms after both prednisone and azathioprine were withdrawn) were treated by resuming prednisone usually at doses of 10 mg/day. Azathioprine (50 mg/day) was usually added if aminotransferases did not normalize within a month. After two or three relapses occurred when the patient was off medication, maintenance doses of medication were usually continued indefinitely and consisted of prednisone alone (9.1 ± 6.0 mg/day) or combinations of prednisone (10 ± 8.1 mg/day) and azathioprine (67 ± 27 mg/day).

Results

All but six patients underwent one or more relapses during the follow-up period. These relapses often occurred during life situational periods of stress (death in the family; change or loss of job; difficulties with children as examples). Recrudescences (exacerbation on therapy) were also often associated with similar stressful life experiences.

For the 36 patients who sustained relapses, the average number of relapses off medication was 3.3/patient and ranged as high as eight relapses for one patient who has been followed for 43 years. The incidence of relapses with time of follow-up is illustrated in the figure. As noted, there was no correlation between the number of relapses and the duration of the disease or treatment. Most relapses were readily treated by resuming prednisone and azathioprine. After 2–3 relapses low-dose immunosuppression was continued indefinitely.

Seven patients (16.6%) had other associated autoimmune diseases, two with ulcerative colitis, one with Crohn's disease, two with thyroid disease (hypothyroidism and Hashimoto's thyroiditis) and one with lupus erythematosis. One patient was thought to have an overlap syndrome with primary biliary cirrhosis. This patient had a positive anti-mitochondrial antibody titer of 1:640 and responded to ursodeoxycholic acid as well as immunosuppressive therapy. Another patient, who also had active ulcerative colitis, had an overlap syndrome with primary sclerosing cholangitis, diagnosed by endoscopic retrograde cholangiography. The seven patients with associated autoimmune disorders had a mean of 1.6 relapses (up to 3/patient) compared with 1.7 episodes for the others (up to 8/patient). Only one of these seven patients progressed to cirrhosis and none developed signs of liver failure.

At the time of this long-term follow-up, 36 patients (85.7%) have responded well to treatment (Table 3). The serum alanine aminotransferase transaminase was normal in all but eight patients. Only five patients have serum albumin levels <3 g% or elevations in the serum alkaline phosphatase. Serum bilirubin was increased in only six patients, ranging from 1.3 to 3.8 mg%. Seven patients are on low doses of diuretics, two for cardiovascular complications and none of these patients have clinical evidence of ascites. Current therapy consists of prednisone alone in six patients (14.28%), azathioprine alone in three (7.1%), and azathioprine in combination in 28 patients (66.6%). Five of the 42 patients are currently being followed without immunosup-

pression. These five patients have been followed from 8 to 31 years with a mean follow-up of 20.2 years. They have been off immunosuppressive therapy from 4 to 9 years with a mean time of 5 years. Six Child Class B or C patients (14.28%) have been evaluated for liver transplantation, three because they developed early signs of hepatic encephalopathy, one because of esophageal hemorrhage requiring a transhepatic intraperitoneal stunt, one because of refractory recurrent hydrothorax, and one because of persistent ascites. To date only one of these patients has received a liver transplant; four other patients with lower MELD scores are listed and continue to be maintained as outpatients. One patient died with refractory ascites and sepsis after submission of this report. Table 4 illustrates the clinical features including duration of follow-up of these six patients.

Progression to advanced chronic liver disease (cirrhosis) was assessed in all patients by a combination of studies that included liver biopsies in 20 patients, screening endoscopy for the development of varices in 25 patients and Tc-sulfur colloid scans in 25 patients. Follow-up studies for esophageal varices revealed grade 1–2 varices in only seven patients (16.7%). Thus, many patients in the cohort (18/25) have remained free of varices over this long period of follow-up. Radionucleotide liver spleen scans were normal in 12 patients (28.5%), they demonstrated mild colloid shift in six patients (14.3%), moderate colloid shift in five patients (11.9%) and evidence of marked shift in only two patients (4.7%). On the basis of these studies a presumptive clinical diagnosis of cirrhosis was based on liver biopsy in 11 cases, liver spleen scans in three cases and evidence of varices in six others.

Long-term side effects of corticosteroid therapy were minimal for most of these patients. The most common problem was weight gain, which was observed in nine patients (21.4%) while three patients developed cushingoid features, two of whom considered this side effect significant (7.1%). Serious side effects have occurred in two patients, one who developed cryptococcal meningitis but has fully recovered, and one with aseptic necrosis of the hip. Two patients developed steroid-related osteoporosis (4.7%). Two other patients had evidence of osteoporosis on a DEXA scan, but they were older patients and aging was thought to account for these findings. Remarkably, none of the patients in this cohort have developed steroid-induced diabetes. Four of the patients in this cohort have transferred their medical care to other hospitals because of relocation. Follow-up information for these patients was obtained from those facilities and outcomes were similar to those that remain at Yale.

Table 3. Liver function tests at last follow-up

# Patients with abnormal ALT	8 (19%)
(#>2 × normal)	1 (2.7%)
# Patients with abnormal AST	11 (26%)
(#>2 × normal)	0
# Patients with abnormal bilirubin (range 1.3–3.8 mg%)	6 (14.28%)
# Patients with INR>1.1	6 (14.3%)
1.2–1.35	5 (11.9%)
1.6	1 (2.3%)
# Patients with abnormal alkaline phosphatase	3 (7.1%)
(#>2 × normal)	0
# Patients with abnormal albumin levels (%)	
(2.0–3.4 g)	9 (21%)
>4.0 g	24 (57%)
3.5–3.9 g	9 (21.4%)
3.0–3.4 g	4 (9.5%)
2.5–2.9 g	2 (4.7%)
2.0–2.4 g	3 (7.1%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Discussion

This study reports the results of prolonged medical therapy with immunosuppression in a cohort of 42 patients with AIH followed at the Yale Liver Center for a mean of 16 years. Medical therapy has continued in this group over a period of 7–43 years. All of the patients in this cohort,

Table 4. Characteristics of patients referred to liver transplantation

			Medications		No.of relapses	Current Parameters								
Sex	Age	Follow-up (years)	Initial	Present	Total	AST (IU)	ALT (IU)	PT/INR (Sec)	Bilirubin T/D (mg%)	Alk Phos (IU)	Alb (g%)	Bleeding varices	Ascites	Hepatic encephalopathy
F	52	35	NA	Off Rx since 1998	2	86	52	14/1.35	2.12	142	2.8	Yes	Yes	Yes
F	66	31	40 P	5 P & 50 I	4	58	14	12.1/1.2	2.6/0.6	116	2.8	No	Yes	Yes
F	36	23	NA	15 P & 50 I	1	140	35	NA	0.77/.36	259	3.3	No	Yes	Yes
F	28	7	30 P 1993	12.5/15 P QOD	1	60	28	11.6	3.8/1.34	62	2.3	Yes	Yes	Yes
F	68	35	NA	2.5P & 50 I	1	30	21	12.6/1.5	2.3/0.3	71	2.8	No	Yes	No
F	59	33	NA	7.5P & 50 I	2	55	76	NA	2.56/0.62	54	NA	Yes	No	No

NA, not available; P, prednisone; I, imuran; PT, prothrombin time; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; Alk Phos, alkaline phosphatase; Alb, Albumin.

with the exception of four patients, have been followed by one of the authors during this period (J. L. B) and therapy has been carefully adjusted on an individual case basis. The cohort is notable in several respects. First, this group of patients represents the longest follow-up data on the effects of long-term continuous immunosuppression in AIH type 1 that is available in the literature to date. A previous study reported the prognosis of a large cohort of 128 patients with AIH followed for a mean of ~ 10 years (6). Secondly, therapy is tapered from maintenance levels and discontinued only after the aminotransferase values are completely within the normal range. This is in contrast to some treatment protocols that accept aminotransferase levels $<2\times$ the normal range as indicating a full remission (2, 6, 7). Despite the prolonged duration of immunosuppression in our patients, side effects have been minimal and clinically significant in only three patients. Most strikingly, all but six patients are quite stable clinically, with minimal symptoms and normal or minimal abnormalities in tests of liver function. This lack of significant steroid side effects in most patients in this study is probably the result of highly individualized rather than protocol-based therapy that included multiple efforts to reduce the dosage of corticosteroids to the minimal level required to maintain normal serum amino transaminases as well as repeated attempts to discontinue immunosuppression whenever possible. This effort is reflected in the relatively high number of biochemical and clinical relapses in some patients (Fig. 1), all but a few of whom have rapidly responded to resumption of immunosuppression therapy. A similar high frequency of relapses has also been reported by others after treatment withdrawal (26, 27) Nevertheless, once 2–3 relapses have occurred, continuous treatment with small doses of prednisone and azathioprine was usually advised because of concern for further relapses.

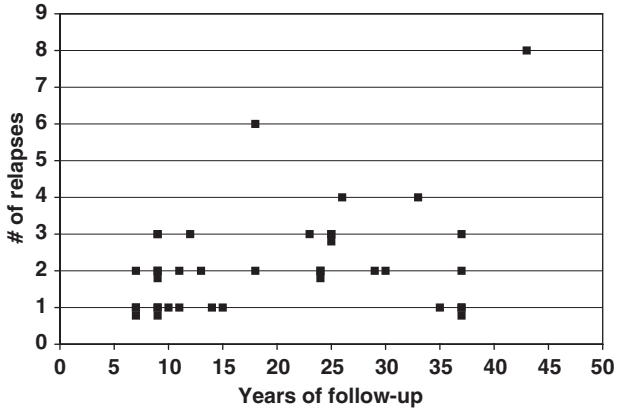

Fig. 1. Number of relapses for each of the 36 patients plotted as a function of their duration of follow-up in years.

These clinical responses to therapy also emphasize the well-known observation that classical cases of AIH are normally quite responsive to low doses of immunosuppression (28). Indeed, serum alanine aminotransferase values are currently within normal range in 34 (81%) patients in this cohort while five patients (11.9%) have discontinued medication without any subsequent clinical or biochemical relapses 4–9 years after stopping therapy. In this setting, complications of chronic liver disease such as clinically significant portal hypertension (esophageal varices and/or moderate or severe colloid shifts on liver spleen scans) have been modest. Five of the 42 patients have developed significant chronic fluid retention (ascites) and only four have symptoms attributable to hepatic encephalopathy. Six patients have been evaluated for liver transplantation, but only one patient has received a transplant.

To what extent are the patients in this cohort typical of this disease and to what extent has selection bias been responsible for their favorable long-term medical management? Since we arbitrarily excluded patients who had been followed for less than 7 years in order to concentrate on a cohort with long-term follow-up, we cannot exclude the possibility that patients with a more progressive course may have been excluded from this study if they died or required liver transplantation within a 7-year period from the onset of the disease. However, this has not been our experience. Indeed, all of the included patients fulfilled the diagnostic criteria for 'definite AIH type 1' as classified by the International Autoimmune Hepatitis Group (25) and many of these patients were clinically decompensated when initially referred (see Table 2). Furthermore, those with the longest follow-ups (20 years or more) were referred to us before the availability of liver transplantation. Twenty patients (47.6%) have presumptive clinical evidence of progression to cirrhosis as judged by biopsy, liver spleen scans or development of esophageal varices, and this figure could be an underestimate. Nevertheless, the Yale Liver Center serves both a university and community referral base and it is possible that referrals to this Center may be biased by patients with less advanced disease on entry who are more likely to respond favorably to medical therapy. Indeed, other reports described clinical deterioration in 13–20% of patients on similar immunosuppressive regimens (6, 22). While we can not assess whether the patients in our study are representative of the average response to immunosuppression, this cohort clearly demonstrates

that many patients with AIH type 1, including those with cirrhosis, can be managed for decades with low dose immunosuppression without signs of clinical decompensation. The study also supports previous observations that AIH patients with cirrhosis also respond well to immunosuppression (5–7). In addition, despite the long-standing medical therapy, hepatocellular carcinoma has not developed in any of our patients as reported by others (27). Together, these findings indicate that it is possible to manage many patients with chronic active AIH medically for three or four decades despite initial decompensation without development of significant complications or the need for transplantation. Our findings support a conservative medical approach to management in this disease as long as possible, particularly given the significant mortality and morbidity and the high incidence of recurrence of disease in patients undergoing liver transplantation for AIH.

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