Sustained remission after treatment withdrawal in autoimmune hepatitis: a multicenter retrospective study

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INTRODUCTION

The treatment of autoimmune hepatitis (AIH) is based on immunosuppressive drugs. First-line induction regimen usually combines corticosteroids and azathioprine. Full biochemical response is defined as normalisation of both serum aminotransferase and gammaglobulin or IgG levels.[1,2] After complete biochemical response, the optimal duration of maintenance treatment is not established. It is recommended that it be maintained for at least 2 years.[1,2] However, a remission period of at least 4 years has been reported to reduce further the risk of relapse compared to shorter treatments.[3] In addition, more drastic biochemical response criteria have been reported to predict a lower risk of relapse.[4] Finally, histological response i.e. absence of interface hepatitis at the time of treatment withdrawal has been associated with a lower risk of relapse.[5]

AIM

Main objective : to assess the relapse rate after discontinuation of treatment in AIH patients with prolonged biochemical response and to identify the factors associated with relapse.

Secondary objectives : to identify the predictive factors of histologic remission and to evaluate the evolution of hepatic fibrosis.

METHOD

This multicenter retrospective study was conducted in 5 University Hospitals and 2 private practice centers from France. The medical files of consecutive patients diagnosed as having type 1 AIH were reviewed. Patients were included if they: 1) fulfilled the revised IAHG criteria for the diagnosis of definite or probable AIH 2) had a sustained biochemical remission on first-line immunosuppressive therapy as defined in AASLD and EASL guidelines[1,2] 3) had a liver biopsy following sustained biochemical remission or stopped treatment without liver biopsy according to the decision of the physician in charge of the patient. Relapse was defined as any elevation of serum aminotransferase or gammaglobulin/IgG levels. Relapse rate was analyzed using Kaplan-Meier method. Predictive factors of histologic remission were analyzed by univariate and multivariate logistic regression.
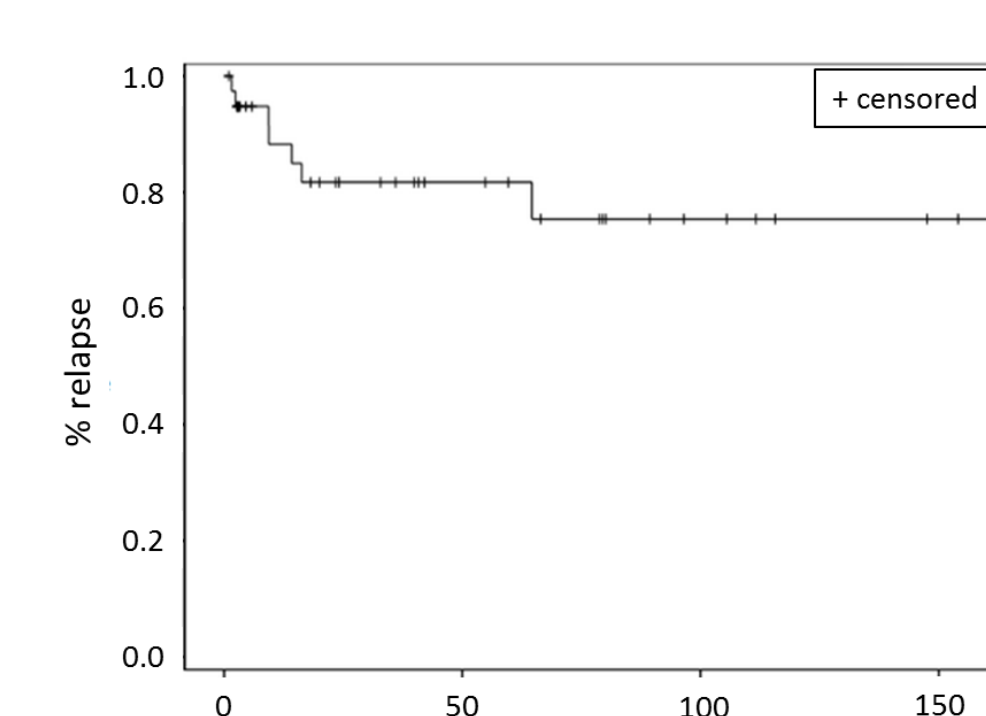
RESULTS

Flow chart of the study
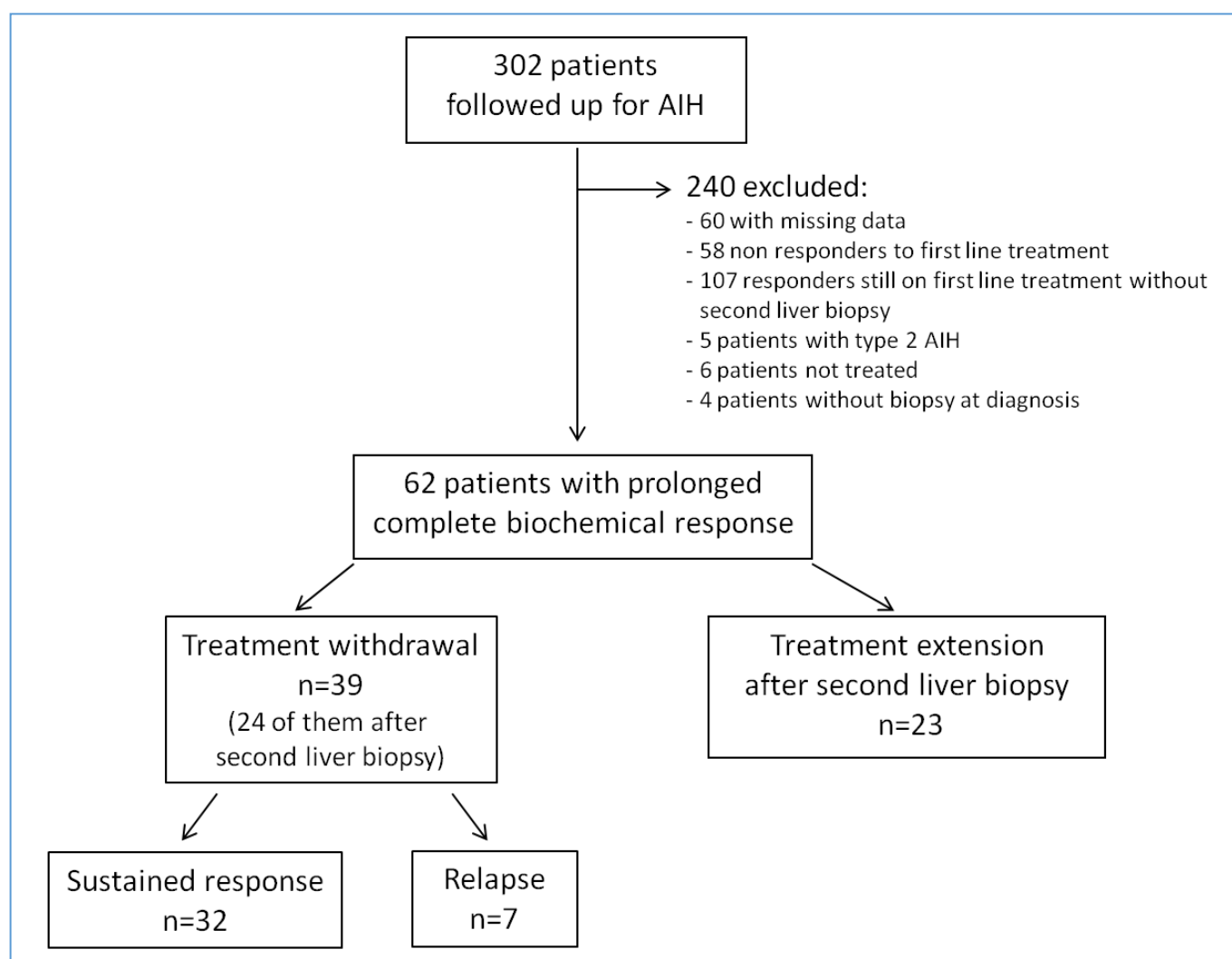
Baseline data in 62 AIH patients

Variables	
Age at diagnosis, years, median (range)	44 (11-73)
Sex ratio, Females/males	47/15 (76/24)
Jaundice md: 2	26 (43.3)
Trigger factors*	5 (8.1)
Other auto-immune diseases	17 (27.4)
Overlap syndrome HAI-CBP	5 (8.1)
Score IAGH, probable/certain	17/45 (27/63)
Biochemical data, median (range)	
ALT, x ULN, md: 1	12.1 (1.4-81)
AST, x ULN, md: 2	7.9 (1.1-56.3)
GammaGT, x ULN, md: 4	4.6 (1-21.5)
Alk. Phosp., x ULN, md: 6	1.3 (1-6.3)
Bilirubin, μmol/L, md: 5	28 (4-467)
Prothrombin rate, %, md: 8	87.5 (23-100)
Albumin, g/L, md:14	39 (22-50)
Platelets, G/L), md: 10	254 (109-545)
γ-globulins, x ULN, md: 34	1.2 (0.8,1.9)
IgG, x ULN, md: 34	1.4 (0.5-2.2)
Auto-antibodies:	
ANA	50 (80.6)
ASMA md:1	35 (56.4)
AMA md:2	5 (8.5)
Anti F-actine md: 37	9 (36)
Anti-LKM md: 8	1 (1.8)
AMA md:2	5 (8.3)
METAVIR A: A0/A1/A2/A3	0/9/19/34
METAVIR F: F0/F1/F2/F3/F4	3/13/21/15/10
Type of treatment	
CT monotherapy	6 (9.7)
CT-azathioprine	55 (88.7)
CT-mycophenolate mofetil	1 (1.6)

The cumulative rate of relapse was 12 % at 12 months and 25% at 64 months. Only one patient with Metavir score A0 at treatment withdrawal relapsed, Other relapsers were two patients Metavir A1 and 4 patients who didn't have liver biopsy before treatment withdrawal.

Kaplan Meier plot: Probability of relapse after drug withdrawal in 39 AIH patients with biochemical remission for a median time of 48 months

Among the 62 included patients, 47 had a biopsy after a median treatment duration of 65.5 months (range 21.3-268.9). Twenty-five (53%) were Metavir A0 and 22 (47%) ≥ A1. Multivariate analysis showed that independent predictors of histological remission were older age (OR1.11 CI95%(1.03;1.2) P=0.007), mild to moderate fibrosis at diagnosis (OR=8.06 CI95% (1.39;47.62) p=0.02) and AST level < 0.6 x ULN at the time of control biopsy (OR=7.05 CI95% (1.35;36.7) p=0.02). Regarding the course of fibrosis, the degree of fibrosis decreased in 26 patients (55%), was stable in 20 patients (43%) and worsened in only one patient (2%). Globally, there was a significant improvement in the level of fibrosis (p = 0.007)

Comparisons of demographics, clinical, laboratory and histopathological data and treatment characteristics between patients with sustained remission and relapsers

	Sustained remission group (n= 32)	Relapse group (n= 7)	p value
Age at diagnosis (years), median (range)	51 (16-73)	44 (25-64)	0.54
Sex ratio, Females/males	25/7(78/22)	4/3(57/43)	0.31
Other auto-immune diseases	8 (25)	1 (14.3)	0.6
Biochemistry at diagnosis, median (range)			
ALT, x ULN, md: 1	16.3 (1.4-81)	12.3 (4.2-30.7)	0.44
AST , x ULN, md: 2	10.7 (1.1-56.3)	5.7 (2.6-37.1)	0.38
γ-globulin, x ULN, md: 23	1.2 (0.8-1.9)	1.1 (0.9-1.2)	0.75
IgG, x ULN, md: 22	1.4 (0.5-2.1)	1.2 (1.1-1.6)	0.94
Autoantibodies at diagnosis			
ANA	25 (78)	7 (100)	0.18
ASMA	16 (50)	7 (100)	0.005
METAVIR Activity (Liver biopsy 1): A0/A1/A2/A3	0/5/9/18	0/1/2/4	0.96
METAVIR F (Liver biopsy l): F0F1/F2/F3F4	9/14/9	1/2/4	0.39
Biochemistry at treatment withdrawal , median (range)			
ALT, x ULN, md: 1	0.5 (0.2-1.0)	0.5 (0.3-0.6)	0.47
AST, x ULN, md: 1	0.6 (0.4-0.9)	0.6 (0.4-0.8)	0.62
γ-globulins, x ULN, md: 21	0.8 (0.6-1.0)	0.7 (0.6-0.7)	0.18
IgG, x ULN, md: 17	0.7 (0.2-1.0)	0.9*	-
Liver biopsy 2	20 (62.5)	4 (57)	
METAVIR A (Liver biopsy 2): A0/A1	19/1	2 /2	0.06
METAVIR F (Liver biopsy 2): F0F1/F2/F3F4	11/9/0	3/0/1	0.10
Treatment			0.82
CT monotherapy	4 (12.5)	1 (14.3)	
CT-azathioprine bitherapy	28 (87.5)	6 (85.7)	
Duration of biochemical remission, median (range) md: 4**	51.9 (20.3-157.8)	44 (25.7-74.7)	0.19
Duration of CT treatment, median (range)**	13 (1.8-268.9)	16.7 (9.2-81.6)	0.91
Duration of azathioprine treatment, median (range) md: 5**	62.7 (27.6-266.4)	44.2 (28.3-67)	0.055
Duration of treatment, median (range)**	66.3 (25.3-269.5)	53.3 (39.5-81.6)	0.14

Data are expressed as No (%) unless otherwise indicated. Continuous variables are reported as median (range). ALT: alanine aminotransferase; AST: aspartate aminotransferase; Alk. Phosph.: alkaline phosphatase; ULN: upper limit of normal; ANA: antinuclear antibody; ASMA: anti-smooth muscle antibody; md: missing data; A:activity; F: fibrosis; liver biopsy 1: at diagnosis; liver biospsy 2: at the end of first line treatment; CT: corticoid. * only one dosage was available in this subgroup. ** duration in months

Comparisons of Demographics, clinical, laboratory and histopathological data and treatment characteristics between patients with and without histological response

	Metavir A0 group n=25	Metavir A≥1 group n=22	p value	OR	Multivariate analysis (IC95%)	p
Age at diagnosis (years), median (range)	49 (20-64)	36 (11-69)	0.007	1.11	[1.03; 1.19]	0.007
Sex ratio (Females/males)	19/6 (76/24)	16/6 (72/28)	0.80			
Other auto-immune diseases	8 (32)	6 (27)	0.72			
Biochemical data at diagnosis						
ALT, x ULN, median (range)	12.1 (2-81)	6 (1.5-38.6)	0.21			
AST, x ULN, median (range) md:1	8.3 (1.1-46)	4.5 (1.2-39.6)	0.66			
γ-globulins, x ULN, median (range) md:22	1.1 (0.8-1.9)	1.1 (0.8-1.7)	0.79			
IgG, x ULN md:28 (n=19)	1.7 (0.5-2.1)	1.2 (0.9-2.1)	0.77			
ANA	22 (88)	16 (72.7)	0.27			
ASMA	13 (52)	12 (27.8)	0.86			
METAVIR Activity (Liver biopsy 1)			0.51			
METAVIR F (Liver biopsy 1): < F3 / ≥F3	18 /7	8/14	0.01	8.1	[1.39; 47.6]	0.02
Biochemical data at Liver biopsy 2						
ALT, x ULN, median (range) md :1	0.8 (0.2-1)	0.5 (0.1-1)	0.39	7.05	(1.35;36.7)	0.02
ASAT < 0.6 x ULN md:2			0.02			
Yes	14(58.3)	5 (23.8)				
No	10 (41.7)	16 (76.2)	0.03			
γ-globulins, x ULN, median (range) md: 22	0.7 (0.6-1)	0.9 (0.6-1)	0.67			
IgG, x ULN md: 22	0.7 (0.6-1.1)	0.76 (0.5-1)				
Type of treatment			0.49			
Corticoid monotherapy	2 (8)	0 (0)				
Corticoid/AZT bitherapy	23 (92)	22(100)				
Delay to transaminases normalization, median (range)	4.3 (0.5-138.8)	7.8 (0.5-49.4)	0.37			
Delay to biochemical remission, median (range) md: 5	7.1 (0.9-138.8)	10.9 (0.5-49.4)	0.96			
Duration of biochemical remission, median (range) md: 5	48.8 (20.8-151.7)	51.8 (0-115)	0.97			
Duration of corticoid treatment, median (range)	11.6 (3.4-268.9)	12.1 (2.3-125.9)	0.89			
Duration of AZT treatment, median (range) md: 2	60.9 (25.8-266.4)	66.1 (20.5-125.9)	0.63			
Duration of treatment, median (range)	64 (25.8-268.9)	70.9 (21.3-126.3)	0.92			

Data are expressed as No (%) unless otherwise indicated. Continuous variables are reported as median (range). ALT: alanine aminotransferase; AST: aspartate aminotransferase; Alk. Phosph.: alkaline phosphatase; ANA: antinuclear antibody; ASMA: anti-smooth muscle antibody; antiLKM: anti-liver/kidney microsomal antibody; ULN: upper limit of normal; md: missing data; A:activity; F: fibrosis; AZT : azathioprine.

CONCLUSIONS

This study shows that the relapse rate after treatment withdrawal in AIH patients may be lowered at approximately 25% at 5 years when the treatment is stopped after a prolonged period of biochemical remission and a complete histological response. Older age, mild to moderate fibrosis at diagnosis and serum AST levels in the lower range of normal at the time of control biopsy are independent predictors of histological response. In addition, we confirm that immunosuppressive treatment of AIH not only prevents further progression of the disease in biochemical responders but allows significant regression of fibrosis even in cirrhotic patients

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