Outcome after Discontinuation of Immunosuppression in Children with Autoimmune Hepatitis: A Population-Based Study

Mark Deneau, MD, MS[1], Linda S. Book, MD[2], Stephen L. Guthery, MD, MS[2], and M. Kyle Jensen, MD, MS[2]

Objective To assess sustained immunosuppression-free remission (SIFR) in children with autoimmune hepatitis (AIH).

Study design We retrospectively reviewed all children with AIH in the region between 1986 and 2011 using a population-based methodology.

Results We identified 56 children with AIH (62.5% females; median age, 11.1 years [IQR, 5.7-14.4 years], followed for a median of 5.6 years [IQR, 2.8-8.6 years]). Liver disease was characterized by type II AIH in 8.9%, cirrhosis in 14.0%, and primary sclerosing cholangitis in 21.4%. Coexisting nonhepatic immune-mediated diseases occurred in 37.5%. Biochemical remission on immunosuppressive therapy was achieved in 76.4% of all patients with AIH at a median of 1.2 years (IQR, 0.4-3.6 years); 23.1% of these patients experienced a subsequent relapse. Discontinuation of all immunosuppressive medications was attempted in 16 patients and was successful in 14 patients (87.5%) with type 1 AIH (median age at discontinuation, 8.9 years [IQR, 3.5-17.9 years], treated for a median of 2.0 years [IQR, 1.3-3.5 years] after diagnosis), with SIFR occurring at a median of 3.4 years (IQR, 2.6-5.8 years) of follow-up. Excluding patients with inflammatory bowel disease who received immunosuppressive therapy independent of their liver disease, the probability of achieving SIFR within 5 years of diagnosis of AIH was 41.6% (95% CI, 25.3%-62.9%). Baseline patient characteristics associated with an inability to achieve biochemical remission on immunosuppression or SIFR were elevated international normalized ratio, positive antineutrophil cytoplasmic antibody titer, cirrhosis, and a nonhepatic autoimmune disorder.

Conclusion We found a high rate of successful discontinuation of all immunosuppressive medications in carefully selected patients with AIH in a population-based cohort. SIFR is an achievable goal for children with AIH, particularly those with type I disease in stable biochemical remission on immunosuppressive therapy. *(J Pediatr 2014;164:714-19)*.

Autoimmune hepatitis (AIH) is a rare, chronic, immune-mediated liver disease with a reported incidence and prevalence of 0.4 and 3.0 per 100 000 children, respectively.[1] Up to 45% of patients with AIH are diagnosed with a concurrent immune-mediated illness, particularly celiac disease, autoimmune thyroid disease, inflammatory bowel disease (IBD), and primary sclerosing cholangitis (PSC).[2-9] Long-term remission can be achieved in the majority of patients with the use of immunosuppressive medications. A subset of patients remains in remission after careful withdrawal of all medications.[10-12]

Most existing data on sustained immunosuppression-free remission (SIFR) success, treatment failure, and associated clinical predictors are derived from single-center reports. There are few descriptions of AIH from population-based cohorts. The aim of the present study was to describe the outcomes of children with AIH from a population-based cohort, with an emphasis on SIFR success rate, as well as the impact and prevalence of nonhepatic autoimmune conditions. We hypothesized that SIFR success rate would be higher in a population-based cohort than in previous single-center descriptions, and that baseline clinical factors would affect the probability of treatment outcomes.

Methods

The state of Utah provides a unique opportunity to study pediatric liver disease in a population-based manner. All of the pediatric and adult hepatologists, all 3 tertiary referral hospitals, and all 3 liver transplantation programs in a geographically isolated region of the western US

AIH	Autoimmune hepatitis
ANCA	Antineutrophil cytoplasmic antibody
ASC	Autoimmune sclerosing cholangitis
IBD	Inflammatory bowel disease
INR	International normalized ratio
PSC	Primary sclerosing cholangitis
SIFR	Sustained immunosuppression-free remission
TSH	Thyroid-stimulating hormone
TTG	Tissue transglutaminase

From the [1]Section of Pediatric Gastroenterology, Department of Pediatrics, University of Manitoba, Winnipeg, Manitoba, Canada and [2]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of Utah, Salt Lake City, UT

Supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (NIH; 8UL1TR000105 [formerly UL1RR025764]). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.12.008

reside within 2 large healthcare organizations. We previously identified all cases of AIH, autoimmune sclerosing cholangitis (ASC), and PSC in a population-based fashion by reviewing medical records from both healthcare organizations between January 1, 1986, and December 31, 2011. All patients with ASC met individual diagnostic criteria for both AIH and PSC. Patients with ASC were counted as patients with AIH in this study. The presence of comorbid PSC was used as a predictor variable in the statistical analysis.

We used data from electronic records from all inpatient, outpatient, and procedure encounters. We examined all laboratory values for biochemical evidence of hepatitis, cholestasis, bile duct injury, or hypergammaglobulinemia (serum total protein minus serum albumin ≥3.85). We included available serum titers for antinuclear antibody, antineutrophil cytoplasmic antibody (ANCA), smooth muscle antibody, and liver-kidney microsomal antibody; hepatitis A, B, and C serology; and histology reports from liver biopsy analysis. We used a simplified adult diagnostic scoring tool[13] that has been validated in children[14] to confirm the diagnosis of AIH (Table I). All research activities were approved by the Institutional Review Board of each healthcare organization.

We excluded patients who were aged >18 years at the time of diagnosis of liver disease, and 1 patient with de novo post-transplantation AIH. We defined celiac disease as an elevated tissue transglutaminase (TTG)-IgA level with Marsh grade II or higher on duodenal histology.[15] Autoimmune thyroid disease was defined as abnormal thyroid stimulating hormone (TSH) level and the presence of antithyroid antibodies in serum. For other autoimmune conditions, we relied on the treating subspecialist's documentation of the appropriate workup and diagnosis, with mention in at least 2 clinical encounters. We classified AIH as drug-induced if symptoms and serum transaminase anomalies appeared after initiation of a new medication implicated in AIH.

We created a retrospective cohort of all children with AIH and followed them from the date of diagnosis to endpoints of biochemical remission on immunosuppression, SIFR, and treatment failure (Table II). All patients underwent a repeat liver biopsy before discontinuation of immunosuppression was attempted. After histopathological confirmation of absence of inflammation, all immunosuppressive medications were tapered and then discontinued over a period of 4-8 weeks. All observations were censored at the end of the review period (March 31, 2013) or at the date of the last clinic visit for patients lost to follow-up.

The Kaplan-Meier method was used to determine 5-year outcome probabilities. The time variable was calculated from the date of liver disease diagnosis. For calculations related to the SIFR outcome, only patients who met all of the following criteria were included: 2 years of follow-up data (at least 1 year of immunosuppression followed by at least 1 year of successful remission while off immunosuppression) and the absence of nonhepatic autoimmune diagnosis necessitating immunosuppressive treatment (eg, Crohn's disease) independent of the AIH diagnosis. Twenty-one patients were excluded. For the biochemical remission on immunosuppression endpoint, only patients with laboratory data available for at least every 3 months through the end of follow-up were included; 5 patients were excluded.

All patients were included in calculations related to the treatment failure endpoint. We analyzed the association between the 3 main clinical outcomes and 8 baseline variables present at the time of AIH diagnosis. Variables were selected based on previously reported associations[3,6,8,16] and anecdotal observations from our previous study.[1] To adjust for confounding, multivariate exact Poisson regression was used to calculate incidence rate ratios. All variables were included in the multivariate (adjusted) analysis regardless of their significance level in the univariate (unadjusted) analysis. All calculations were performed with Stata version 11 (StataCorp, College Station, Texas).

Table I. Simplified scoring system for AIH

Variable	Cutoff	Points
Autoantibodies		
ANA or SMA	1:40	1
	≥1:80	2
LKM	≥1:40	2
SLA	Positive	2
IgG or globulin fraction	>ULN (>3.5 g/dL)	1
	≥1.1 times ULN (≥3.85 g/dL)	2
Liver histology	Compatible with AIH*	1
	Typical of AIH†	2
Absence of viral hepatitis	Yes	2

ANA, antinuclear antibody; *LKM*, liver-kidney microsomal antibody; *SLA*, soluble liver antigen; *SMA*, smooth muscle antigen; *ULN*, upper limit of normal.
Maximum points for all autoantibodies is 2, and total possible points are 8; 6 points indicates probable AIH; ≥7 points, definite AIH.
*Chronic hepatitis with lymphocytic infiltration, without all of the features considered typical.
†Interface hepatitis, lymphoplasmocytic infiltrates in portal tract extending into lobule, emperipolesis, and hepatic rosette formation.

Results

We identified 56 patients with AIH (62% females), diagnosed at a mean age of 10.1 years (range 0.7-17.6 years) (Table III). Acute liver failure was present in 5 patients at initial presentation, representing 9.8% (5 of 51) of patients with AIH with initial international normalized ratio (INR) data available in the medical record. Drug-induced AIH was identified in 7.1% of patients (4 of 56). All 4 patients were adolescent females treated for acne vulgaris. Three of these 4 cases were associated with minocycline, 2 of which required immunosuppression despite minocycline discontinuation, and 1 case was associated with isotretinoin.

Nonhepatic Autoimmune Diseases

IBD was identified in 19.6% of the patients with AIH (11 of 56), including 7 cases of ulcerative colitis and 4 cases of Crohn's disease. PSC was identified in 21.4% of the patients with AIH (12 of 56), and occurred with IBD in 9 of these 12 cases (75%). PSC was obvious on histology in 7 patients; of the remaining 49 patients, 6 (12.2%) underwent cholangiography, which revealed PSC in 5. Additional nonhepatic autoimmune diseases were identified in 21.4% of the patients with AIH