

AZATHIOPRINE FOR LONG-TERM MAINTENANCE OF REMISSION IN AUTOIMMUNE HEPATITIS

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Abstract *Background.* In most patients with autoimmune hepatitis, remission can be maintained with prednisolone, usually in combination with azathioprine, but the majority of patients have a relapse when treatment is stopped and therefore require long-term therapy. Because prolonged corticosteroid therapy may have serious toxic effects, in 1984 we undertook a controlled trial of maintenance therapy with azathioprine alone. None of the 25 patients in that trial had relapses during the follow-up period of one year. We have now followed these 25 patients for 10 years and have treated an additional 47 patients in a similar manner.

Methods. The 72 patients (median age, 47 years; range, 14 to 71) had been in complete remission for at least one year with 5 to 15 mg of prednisolone per day and 1 mg of azathioprine per kilogram of body weight per day. The dose of azathioprine was increased to 2 mg per kilogram per day, and the prednisolone was gradually withdrawn. Remission was defined as the absence of symptoms suggestive of a relapse and serum globulin and aspartate aminotransferase concentrations within the normal range, with or without a liver biopsy showing only minimal inflammation.

Results. Sixty patients (83 percent) remained in remis-

sion while receiving azathioprine alone for a median of 67 months (range, 12 to 128). Of 48 follow-up liver biopsies in 42 patients, 45 showed inactive or minimal disease, and 3 showed moderate disease (2 after one year of therapy and 1 after eight years). After the prednisolone had been withdrawn, 26 patients lost their cushingoid facies, and 32 patients lost weight (median loss, 6.4 kg; range, 1.5 to 22.3). The most common adverse effect was arthralgia (in 38 patients). With the higher dose of azathioprine, four patients had myelosuppression, defined as a decrease in the leukocyte and platelet counts to less than 4000 and 150,000 per cubic millimeter, respectively. Two of these patients (both with pancytopenia) relapsed when the azathioprine was withdrawn; in the other two, remission was maintained with the resumption of prednisolone. Lymphopenia developed in 32 of 56 patients treated with 2 mg of azathioprine per kilogram per day for more than two years. During follow-up, nine patients died: one of liver failure and eight of causes not directly related to their liver disease.

Conclusions. Many patients with autoimmune hepatitis who have been in complete remission for at least one year with prednisolone and azathioprine can remain in remission with a higher dose of azathioprine alone. (N Engl J Med 1995;333:958-63.)

SINCE the early 1970s corticosteroids, often in combination with azathioprine, have been standard therapy for autoimmune hepatitis.¹⁻⁴ Most patients can be maintained in remission for long periods, but a true cure is rare. Since the majority of patients have a relapse when treatment is withdrawn,^{5,6} prolonged immunosuppressive therapy is usually required. In addition to the well-recognized cosmetic effects of corticosteroids, there is a risk of more severe complications, such as cataracts, diabetes mellitus, hypertension, osteoporosis, and psychosis. Azathioprine can induce myelosuppression and has possible teratogenic and oncogenic effects.⁷

We have conducted three controlled trials of the withdrawal of one or both medications in patients with autoimmune hepatitis who remained in remission for long periods with 5 to 15 mg of prednisolone per day and 1 mg of azathioprine per kilogram of body weight per day. In the first trial,⁵ conducted in 1980, we withdrew both medications in a group of 30 patients. Only 5 of the 30 (17 percent) were still in remission by the end of the 1-year trial period; 3 of these patients subsequently had relapses 1.5, 2, and 11 years after stopping treatment. In the second trial, azathioprine was stopped and prednisolone was continued at maintenance doses (5 to 12.5 mg per day) in 27 patients. The calculated cumulative probability of a relapse within three years was 32 percent in this group of patients, as compared with

6 percent in 23 patients who continued to take both medications.⁸ In 1984, we began a third trial, in which patients received a higher dose of azathioprine (2 mg per kilogram per day) after the withdrawal of prednisolone.⁹ In contrast to the results of the previous trials, no patients had relapses during the one-year follow-up period. Because the side effects of prolonged use of azathioprine at this dose were uncertain, we continued to monitor the patients. We report data from the 10-year prospective follow-up of the first 25 patients undergoing this regimen, as well as data on an additional 47 patients treated in a similar manner.

METHODS

The 72 patients were selected from a total cohort of 101 patients born in the United Kingdom (24 males and 77 females) who met the enrollment criteria, had had regular follow-up examinations at our clinic for at least 3 years (median, 12; range, 3 to 25), and had complete records available. Twenty-nine patients continued to receive prednisolone (21 with azathioprine and 8 without it) for the following reasons: they had not had a complete remission continuously for at least one year with maintenance therapy (11 patients); they had adverse reactions (myelosuppression, rashes, or nausea and malaise) when azathioprine was first introduced, necessitating the discontinuation of the drug (8 patients); they had relapses whenever the dose of corticosteroid was reduced to less than 5 mg per day (3 patients); or they declined to stop taking the corticosteroid (5 patients). In addition, two patients had not received any treatment since 1980.⁵

At presentation, the 72 patients ranged in age from 14 to 71 years (median, 47). All 72 had had hyperglobulinemia, elevated serum aspartate aminotransferase concentrations (normal value, ≤ 50 U per liter), and liver biopsies showing moderate periportal inflammation with piecemeal necrosis or severe inflammation (with bridging necrosis) (Table 1). All the patients met the provisional criteria for the diagnosis of definite or probable autoimmune hepatitis.¹⁰ Sixty-three patients had circulating antinuclear or smooth-muscle autoantibodies

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Table 1. Base-Line Characteristics of 72 Patients with Autoimmune Hepatitis Treated with Azathioprine.

CHARACTERISTIC	VALUE
Sex — M/F	17/55
Age — yr	
Median	47
Range	14–71
Mean (±SD) serum biochemical values*	
Aspartate aminotransferase — U/liter	682±545
Bilirubin — mg/dl	5.4±5.7
Globulins — g/dl	5.0±1.1
Alkaline phosphatase — U/liter	228±135
Autoantibody titers ≥1:40 — no. of patients (%)	
Antinuclear antibodies with or without smooth-muscle antibodies	43 (60)
Smooth-muscle antibodies alone	20 (28)
Liver–kidney microsomal antibodies	2 (3)
Anti–asialoglycoprotein–receptor antibodies†	48 (84)
Cirrhosis on initial liver biopsy — no. of patients (%)	27 (38)
HLA typing — no. of patients (%)‡	
A1-B8-DR3	21 (33)
DR3 with or without A1 or B8	11 (17)
DR4 with or without A1 or B8	24 (38)
Negative for DR3 or DR4	8 (12)

*The normal values are as follows: aspartate aminotransferase, ≤50 U per liter; bilirubin, ≤1.0 mg per deciliter; serum globulins, ≤3.5 g per deciliter; and alkaline phosphatase, ≤120 U per liter. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

†Data were available for 57 patients.

‡Data were available for 64 patients.

(or both) at titers of 1:40 or higher (median, 1:160; range, 1:40 to 1:5120), and two had elevated titers of liver–kidney microsomal antibodies (1:320 and 1:640, respectively). The seven patients who did not have any of these autoantibodies were seropositive for antibodies against the hepatic asialoglycoprotein receptor.¹¹ None of the patients had a history of parenteral exposure to blood or blood products. All were seronegative for hepatitis B surface antigen and for antibodies against the hepatitis C virus. Other possible causes of liver disease were excluded by appropriate investigations. HLA phenotypes were determined in 64 patients, as previously described.^{12,13} The study was approved by the ethics committee of King's College Hospital. All patients provided written informed consent.

The first 25 patients⁹ and the additional 47 patients had had complete clinical, biochemical, and histologic remission with 5 to 15 mg of prednisolone per day and 1 mg of azathioprine (Imuran) per kilogram per day for at least 1 year (median, 22 months; range, 12 to 74) before the prednisolone was withdrawn. The dose of azathioprine was increased to the nearest approximation of 2 mg per kilogram per day obtainable with 25-mg tablets (100 to 200 mg per day). Prednisolone was withdrawn in decrements of 2.5 mg per day every two weeks. Twenty-six of the 72 patients consented to a reduction of the dose of azathioprine to 1.5 mg per kilogram per day for 1 month, then to 1 mg per kilogram per day, after they had been in remission with a dose of 2 mg per kilogram per day for at least 1 year (median, 40 months; range, 12 to 70).

For the purposes of this study, a relapse of hepatitis was defined as a threefold increase in the serum aspartate aminotransferase concentration above the normal value (≤50 U per liter) or, in four cases, a smaller increase (71 to 109 U per liter) with an elevated serum globulin concentration (4.1 to 5.2 g per deciliter; normal value, ≤3.5) and the reemergence of symptoms (increasing lethargy, anorexia, malaise, nausea, abdominal pain, arthralgia or myalgia, or jaundice). Remission was defined as the absence of symptoms suggestive of a relapse and serum globulin and aspartate aminotransferase concentrations within the normal range, with or without a liver biopsy showing only minimal inflammation and no necrosis.

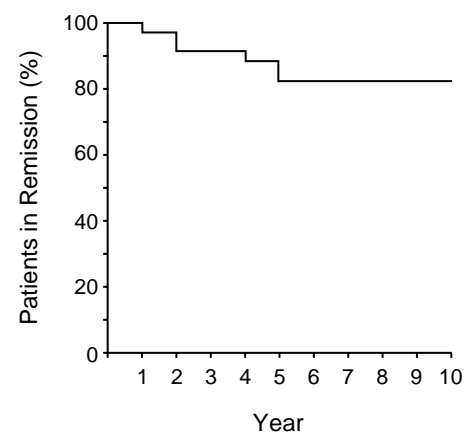
Three main time points were used for the analysis: the date of presentation, the date on which the prednisolone was stopped, and the date of the patient's most recent clinic visit before June 1, 1995, or the date on which treatment with azathioprine alone (2 mg per kilogram per day) was changed, for whatever reason. Statistical analyses were

performed with the paired t-test, the Mann–Whitney U test, or Fisher's exact test, as appropriate.¹⁴ All tests were two-tailed.

RESULTS

Of the 72 patients whose treatment was changed to azathioprine alone at a dose of 2 mg per kilogram per day, 12 had relapses. Seven of the 12 patients with relapses (1 each at 7, 9, 12, 14, 23, 40, and 59 months) had no obvious precipitating factors. Pancytopenia developed in two patients (at six months in one, and at eight months in the other); in both, the dose of azathioprine was reduced to 1 mg per kilogram per day, and both had relapses within a month after the dose reduction. Three patients had relapses with precipitating factors: chickenpox in one patient at 14 months, pregnancy in another patient, and the discontinuation of therapy at 23 months in the third. The other 60 patients (83 percent) remained in remission with azathioprine alone at a dose of 2 mg per kilogram per day for a median of 67 months (range, 12 to 128) (Fig. 1).

Forty-two patients consented to undergo liver biopsies on at least one occasion after one to eight years of treatment with the higher dose of azathioprine (Table 2). One patient had a biopsy at one year that showed moderate disease activity, but clinical and biochemical remission continued for four more years before relapse. A second patient with a biopsy showing moderate activity at one year was still in complete clinical and biochemical remission five years later. A third patient had histologically inactive disease at two years, but another biopsy six years later showed moderate disease activity. She was still asymptomatic, with normal biochemical liver tests, three years after the second biopsy. The bi-



NO. OF PATIENTS

Total eligible for analysis	70	66	59	49	42	38	36	34	31	30
Cumulative total with relapses	2	5	5	6	7	7	7	7	7	7
Cumulative total excluded	2	6	13	23	30	34	36	38	41	42

Figure 1. Kaplan–Meier Analysis of the Cumulative Probability of Sustained Remission during Treatment with 2 mg of Azathioprine per Kilogram per Day in Patients with Autoimmune Hepatitis.

Patients were excluded if they had relapses with precipitating factors or died or if their treatment was changed for any reason other than a spontaneous relapse.

opsies in the other 39 patients showed inactive disease or only minimal inflammation without necrosis. Two patients with minimal activity at 1 year had relapses 2 and 6 years later, within 8 and 24 months, respectively, after the reduction of the dose of azathioprine to 1 mg per kilogram per day.

Changes in Hematologic and Biochemical Variables

Four patients had overt myelosuppression, defined for purposes of this study as a progressive decrease in both leukocyte and platelet counts to values below the lower limits of normal (4000 and 150,000 per cubic millimeter, respectively). In addition to the two patients who had pancytopenia and relapses when the dose of azathioprine was reduced, two patients had myelosuppression after 19 and 22 months, respectively. In both patients, remission was maintained by readministering prednisolone before discontinuing azathioprine; the myelosuppression resolved in both cases. A fifth patient had transient leukopenia that was corrected within three months (without the reintroduction of prednisolone) by reducing the dose of azathioprine to 1 mg per kilogram per day. The leukopenia did not recur when the dose of azathioprine was subsequently increased to 2 mg per kilogram per day. Two other patients had leukocyte counts between 3000 and 4000 per cubic millimeter throughout the study, but no adjustment in the dose of azathioprine was considered necessary. Apart from these seven patients, all the patients had leukocyte counts within the normal range. There was, however, a significant overall decrease in the white-cell count between the start and the end of the study in the patients receiving 2 mg of azathioprine per kilogram per day (Table 3). Ten patients had platelet counts of less than 150,000 per cubic millimeter at the start of the period when the dose of prednisolone was tapered. The thrombocytopenia did not worsen

Table 3. Hematologic and Serum Biochemical Indexes of Cholestasis in 58 of the 60 Patients with Autoimmune Hepatitis Who Did Not Have Relapses with Azathioprine Alone (2 mg per Kilogram per Day).*

INDEX	NORMAL VALUE	TREATMENT WITH AZATHIOPRINE ALONE	
		START	END
<i>mean ±SD</i>			
Hematologic values			
White-cell count (per mm ³)	4000–12,000	6300±2100†	5400±1600†
Hemoglobin (g/dl)	12–18	13.7±1.3	13.4±1.4
Platelet count (per mm ³)	150,000–400,000	212,000±79,000	213,000±84,000
Serum biochemical values			
Alkaline phosphatase (U/liter)	≤120	96±49	86±39
γ-Glutamyltransferase (U/liter)	≤55	59±55	41±33‡
Bilirubin (mg/dl)	≤1.0	0.70±0.35	0.74±0.57
Months of treatment			
Median		67	
Range		12–128	

*The two patients in whom prednisolone was restarted because of myelosuppression have been excluded. The start of treatment with azathioprine alone was defined as the day on which prednisolone was stopped; the end of treatment with azathioprine alone was considered to be the date of a change in treatment or the most recent clinic visit before June 1, 1995. To convert values for bilirubin to micromoles per liter, multiply by 17.1.

†P=0.004, by paired t-test, for the comparison with the value at the start of treatment.

‡P=0.002, by paired t-test, for the comparison with the value at the start of treatment.

(and improved in five of the patients) with the higher dose of azathioprine given alone.

Lymphopenia was a frequent finding. The mean (±SD) lymphocyte count in the 56 patients receiving 2 mg of azathioprine per kilogram per day for at least two years was 1300±500 per cubic millimeter, with 32 patients having counts below the lower normal limit of 1500 per cubic millimeter. These counts were not significantly affected by reducing the dose of azathioprine to 1 mg per kilogram per day (mean lymphocyte counts before and after the dose reduction in 26 patients, 1300±400 and 1400±500 per cubic millimeter, respectively; P=0.19), nor were the counts significantly different from those in the 27 patients who continued to receive either prednisolone alone (1000±500 per cubic millimeter) or combination therapy (1200±500 per cubic millimeter; P=0.47).

There was no evidence that the higher dose of azathioprine induced cholestasis. Between the start and the end of the study, there was a significant reduction in serum γ-glutamyltransferase activity (Table 3).

Effects of Corticosteroid Withdrawal

Forty patients (56 percent) had symptoms associated with the withdrawal of prednisolone; in 38 of the 40, the main symptom was arthralgia affecting the knees, elbows, and fingers. In 30 patients, the arthralgia lasted less than six months and was relieved with mild analgesic treatment (acetaminophen). In eight patients, the arthralgia was more prolonged and severe, requiring the administration of nonsteroidal antiinflammatory drugs. In 10 patients, the arthralgia was accompanied by myalgias (lasting 2 to 10 months; median, 4) affect-

Table 2. Histologic Findings in 48 Liver-Biopsy Specimens from 42 Patients with Autoimmune Hepatitis Treated with Azathioprine Alone (2 mg per Kilogram per Day).

YEARS OF TREATMENT	HISTOLOGIC FINDING*		
	INACTIVE DISEASE	MINIMAL DISEASE	MODERATE DISEASE
<i>no. of patients</i>			
1	5	21	2
2	1	10	
3	1	2	
4		1	
5	1	1	
6			
7	1	1	
8			1

*Inactive disease was defined as no inflammation or hepatocellular necrosis; minimal disease as lymphocytic infiltration confined to portal tracts and immediate periportal areas, without necrosis; and moderate disease as portal and periportal lymphoplasmacytic infiltration with piecemeal necrosis of periportal hepatocytes, without bridging or lobular necroinflammation.

ing the legs and arms. Other symptoms included increased lethargy (in seven patients), nausea for no more than 2 months (in five), diarrhea for no more than 10 days (in three), bilateral Achilles tendinitis for 2 months (in one), a petechial rash lasting 3 weeks (in one), and pruritus for 1 week (in one).

Cushingoid facies (in 26 patients initially) disappeared after the prednisolone had been withdrawn. Thirty-two patients lost 1.5 to 22.3 kg of body weight (median, 6.4).

After one year of therapy with azathioprine alone, the patients were asked, "How do you feel since stopping steroids?" Thirty-six patients, including 15 who had arthralgia, responded that they were "better" or "much better," and 32 said they were "about the same." Four patients said they felt "worse" but did not wish to resume treatment with prednisolone.

Overall Outcome

During the follow-up period, nine patients (all women) died: one of liver failure and eight of causes not directly related to the liver disease (Table 4). Four of the patients died of primary cancers. Another patient, a man with autoimmune hepatitis for seven years, had a lymphoma on his forehead after six years of treatment with azathioprine alone at a dose of 2 mg per kilogram per day. The tumor was excised, and he was given local radiotherapy. No evidence of lymphoma at other sites was found, and he was well two years later. The cumulative dose of azathioprine in the 5 patients with cancer (median, 282 g; range, 198 to 499) was not significantly different from the cumulative dose in the 67 patients without malignant disease (median, 354 g; range, 87 to 734; $P=0.33$).

Three unplanned pregnancies occurred in two patients receiving azathioprine alone at a dose of 2 mg per kilogram per day. One patient had a relapse at 29 weeks' gestation (after 26 months of treatment with the higher dose of azathioprine), and prednisolone was restarted. She had no other problems with her pregnancy and subsequently delivered a healthy baby. The other patient, who had been receiving 2 mg of azathioprine per kilogram per day for 75 months, died of severe pulmonary hypertension at 25 weeks' gestation (Table 4). Four years earlier, while taking the higher dose of azathioprine, she had delivered a healthy baby after an uncomplicated pregnancy.

Of the 26 patients who agreed to have the dose of azathioprine reduced to 1 mg per kilogram per day, 5 had relapses (1 each at 8, 13, 24, 25, and 26 months after the dose reduction), 1 died of a myocardial infarction 1 year after the dose reduction (Table 4), and 14 continued to be in remission for a median of 57 months

Table 4. Data on the Nine Women with Autoimmune Hepatitis Who Died during Follow-up.

PATIENT NO.	AGE AT DEATH	DURATION OF DISEASE*	AZATHIOPRINE THERAPY			CAUSE OF DEATH
			1 mg/kg/DAY	2 mg/kg/DAY	CUMULATIVE DOSE	
			yr	mo	g	
1	57	10	75	26	355	Carcinoma of pharynx
2	27	10	32	75	326	Pregnancy-associated pulmonary hypertension
3	76	12	27	86	303	Carcinoma of stomach and esophagus
4	78	8	15	40	154	Cerebrovascular hemorrhage
5	73	20	62	24	272	Liver failure
6	24	3	12	21	142	Septicemia as a complication of acute Epstein-Barr viral infection
7	65	5	13	43	198	Carcinoma of breast with lung metastases
8	77	6	25	46	171	Myocardial infarction
9	66	8	53	36	238	Carcinoma of lung

*From the first appearance of symptoms or signs.

(range, 24 to 77). The other six patients requested that all treatment be stopped (one each at 6, 18, 20, 24, 25, and 32 months after the dose reduction); two had relapses (one 10 months and one 26 months after stopping treatment), and four continued to be in remission for 6, 8, 46, and 55 months.

Overall, treatment with azathioprine alone (2 mg per kilogram per day) was changed or stopped in 49 of the 72 patients: the dose was electively reduced in 26 patients, and the treatment was altered or discontinued in 23 because of relapses, complications, or death. The other 23 patients remained in remission with the higher dose of azathioprine alone for a median of 109 months (range, 39 to 128). No variables were identified at presentation or subsequently that predicted which patients would remain in remission with either dose of azathioprine alone or in which patients the drug could be withdrawn altogether.

DISCUSSION

In a previous study of 30 patients with autoimmune hepatitis, we found that 25 (83 percent) of those who had a remission with immunosuppressive therapy had relapses within one year after all treatment had been stopped.⁵ Three additional patients had relapses after a longer period of follow-up, for a total relapse rate of 93 percent. The current study indicates that the higher dose of azathioprine alone is a therapeutic option for about 80 percent of patients with autoimmune hepatitis who have had a complete remission for at least one year with maintenance doses of prednisolone and azathioprine. For an individual patient, the most appropriate maintenance regimen depends on the frequency and severity of the side effects associated with these two drugs when taken for both short and long periods. Treatment with azathioprine alone at a dose of 2 mg per kilogram per day reversed the cushingoid facies and weight gain that had been associated with prednis-

olone therapy in 44 percent of our patients (other complications were rare), and most of the patients reported that they felt better (or at least did not feel worse), despite the development of arthralgias after the prednisolone had been withdrawn. The psychological benefit of discontinuing corticosteroid therapy is substantial. We believe that this approach is likely to improve compliance with therapy, particularly among young women.

Most of our patients did not have serious myelosuppression or other toxic effects. Azathioprine has been implicated in the development of nodular regenerative hyperplasia in the recipients of liver, kidney, and bone marrow transplants and in isolated cases of other conditions (multiple sclerosis, myasthenia gravis, and psoriasis).^{15,16} Liver biopsies showed no evidence of such abnormalities in our patients, nor were there the clinical indications of portal hypertension or the biochemical evidence of cholestasis usually associated with nodular regenerative hyperplasia.¹⁵ Since many patients declined a liver biopsy when they were asymptomatic and had normal liver-function tests, we cannot be certain that all the patients had histologic remission. Nonetheless, the data reported here and in our previous study⁹ suggest that the majority of the patients had histologic remission. It is noteworthy, however, that periodic abnormal findings on liver biopsy did not predict relapses (possibly because of a sampling bias). Nevertheless, liver biopsies at two-to-three-year intervals should probably be part of the routine follow-up of patients receiving the treatment used in this study.

Among the patients who had relapses or myelosuppression, the failure to remain in remission with azathioprine alone may have been related to genetic differences in the metabolism of the drug.¹⁷⁻²¹ We found no evidence of two other potential side effects of high doses of azathioprine or long-term treatment with the drug: teratogenesis and carcinogenesis. The incidence of azathioprine-related congenital abnormalities is reportedly very low,²² but experience is limited, and the drug's safety during pregnancy has not yet been fully established.²² The risk to the fetus associated with a relapse of autoimmune hepatitis during pregnancy is much higher than that associated with azathioprine therapy.²³ Nevertheless, our current policy with women who plan to become pregnant while taking azathioprine is to reintroduce, or increase the dose of, corticosteroids and withdraw azathioprine.

There is concern that immunosuppressive therapy, particularly with higher doses of azathioprine, may increase the risk of malignant disease. An increased risk of extrahepatic cancer (odds ratio, 1.4; 95 percent confidence interval, 0.6 to 2.9) was reported in 103 patients with autoimmune hepatitis receiving 50 mg of azathioprine per day, as compared with 103 age- and sex-matched normal persons.²⁴ An increased incidence of both lymphomatous and nonlymphomatous cancers was noted in 202 patients with rheumatoid arthritis receiving very high doses of azathioprine (median dose, 300 mg per day).²⁵ This incidence did not differ significantly from that in patients with rheumatoid arthritis who

did not receive the drug, suggesting that there was some risk associated with rheumatoid arthritis itself.²⁵ Viteri et al.²⁶ have suggested that, like some other diseases in which immune responsiveness is disturbed, autoimmune hepatitis may be associated with an inherently increased risk of malignant disease that is further increased by immunosuppressive therapy. Our data suggest that this additional risk is small. Most cancers associated with immunosuppressive therapy are lymphomas or squamous carcinomas of the skin.²⁷ In our series, there was one lymphoma; the other cancers that developed were those that are common in people in the age range of our patients.

The use of corticosteroids and azathioprine for the treatment of autoimmune hepatitis was developed empirically, but the rationale is now understood. Liver injury in autoimmune hepatitis is probably mediated by antibody-dependent cellular cytotoxic reactions, in which liver-specific autoantibodies cooperate with a subpopulation of non-T lymphocytes (K cells) in damaging hepatocytes, rather than by direct cytotoxic effects mediated by T cells or natural killer cells.²⁸ Prednisolone rapidly suppresses the production of immunoglobulins (including autoantibodies), whereas azathioprine is thought to act on K cells (and natural killer cells), but its effects are manifested more slowly.²⁹⁻³² Indeed, it seems to take up to six months for K cells to disappear from the circulation,³³ which probably explains why remission cannot usually be induced by azathioprine alone and why the drug needs to be administered for several months before its corticosteroid-sparing effect allows the reduction of the dose of prednisolone to low maintenance levels.

In summary, our findings indicate that once complete remission has been induced and sustained with combination therapy for at least one year, prednisolone can be withdrawn, and the majority of patients will remain in remission with azathioprine given alone. After a further period of remission with the higher dose of azathioprine, it is possible in many instances to maintain the remission at the more conventional dose of 1 mg of azathioprine per kilogram per day.

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