Temporal prescribing trends in AIH: Exploring the influence of early thiopurine use on corticosteroid dependency and biochemical response

**Authors:**

Sital Shah1,2 MPharm, Yooyun Chung1 MD, Cathrine McKenzie2,3 MPharm, PhD, Maura Morrison1 MD, Michael A Heneghan1 MD MMedSc, FRCPI

**Affiliations:**

1. King's College Hospital NHS Foundation Trust, Institute of Liver Studies, London, UK
2. King's College London, Institute of Pharmaceutical Sciences, School of Cancer and Pharmacy, Faculty of Life Sciences and Medicine, London, UK
3. University of Southampton School of Medicine, NIHR Biomedical Research Centre, Perioperative, and Critical Care theme and NIHR Wessex Applied Research Collaborative (ARC), Southampton, UK

**Correspondence:**

Sital Shah

Consultant Pharmacist, Hepatology

Institute of Liver Studies, King’s College Hospital NHS Foundation Trust

Denmark Hill, London, SE5 9RS, United Kingdom

Email: sitalshah@nhs.net

Phone: +442032995714

**Keywords:**  azathioprine, corticosteroid, cumulative dose, prescribing, autoimmune hepatitis

**Electronic word count:** 3456

**Conflict of Interest:** None

**Financial Support:** This paper did not receive any funds or grants

**Author contribution:**

SS: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript, critical revision of the manuscript and final approval of version to be published

YC: acquisition of data, statistical analysis, critical review of manuscript and final approval of version to be published

CM: Contribution to design of the work, statistical analysis, critical review of manuscript and final approval of version to be published

MM: acquisition of data, statistical analysis, critical review of manuscript, final approval of version to be published

MAH: Substantial contribution to conception and design, study supervision, critical review of manuscript and final approval of version to be published. Overall guarantor of this study.

**Abstract**

**Objective:** Patients with autoimmune hepatitis (AIH) receive variable corticosteroid and thiopurine regimens. Our aim was to undertake a cohort study to determine whether earlier introduction of azathioprine allowed reduction in cumulative corticosteroid burden. We also determined, temporal trends on treatment choices and outcomes.

**Method:** 226 adults with AIH treated from 1970 - 2020 at Kings College Hospital (KCH), were divided into 2 groups: patients who received azathioprine therapy within 8 weeks of initiation of corticosteroid therapy (early group, n = 106) and patients who had received azathioprine more than 8 weeks after corticosteroid initiation (late group, n = 120).

**Results:** Cumulative exposure to corticosteroid was not significantly different between each group Eighty percent of patients achieved normalisation of AST within 6 months of corticosteroid induction compared to 64.5% in the late group (p= 0.013). When evaluated by decade, the cumulative corticosteroid exposure and dose declined over time (p <0.001). Azathioprine initiation fell from a mean of 80 weeks from corticosteroid induction in the 1970’s to 10 weeks in the 2010s (p = 0.026). Biochemical remission occurred at a faster rate in more recent cohorts (p = 0.001).

**Conclusion:** Earlier introduction of azathioprine after corticosteroid therapy resulted in a higher rate of transaminase normalisation at 6-months but did not significantly reduce the cumulative prednisolone exposure over five years. Temporal effects in the management of AIH is evident whereby earlier introduction of thiopurines in recent decades facilitated more rapid reduction in corticosteroid dose whilst achieving a higher rate of biochemical response.

**Lay Summary:**

**What is already known on this topic:**

• Patients with autoimmune hepatitis receive variable corticosteroid and thiopurine regimens

**What this study adds:**

• There are temporal trends in thiopurine prescribing for AIH management

• Azathioprine was introduced earlier in more recent decades

• There was lower cumulative exposure to prednisolone in recent decades

• Higher rates of biochemical remission occurred in recent decades

**How this study might affect research, practice or policy:**

• To encourage optimal use of limited treatment options for AIH

**Introduction**

Autoimmune hepatitis (AIH) is an inflammatory liver disease which, left untreated, can result in cirrhosis, liver failure and death.1 AIH is characterised by circulating autoantibodies, elevated serum immunoglobulin levels and typical histological features.1 AIH is rare with a prevalence of 16-18 cases per 100,000 individuals in Europe.1 The overall goal of AIH treatment is to induce and maintain suppression of inflammatory activity; thereby preventing disease progression to cirrhosis and liver decompensation. Corticosteroids have been the mainstay of treatment for AIH over the last 50 years. High doses of oral prednisolone are typically prescribed with initial doses between 0.5 - 1 mg/kg to induce remission.1 Early corticosteroid therapy is followed by introduction of thiopurine with tapering of the corticosteroid dose.2

Azathioprine, 1 - 2mg/kg/day, is the thiopurine of choice for maintenance therapy and facilitates withdrawal of corticosteroid, thereby reducing corticosteroid burden and associated side effects.2 However, there remains uncertainty around optimal timing of azathioprine initiation. European and British AIH guidelines recommend delaying introduction of azathioprine by two or more weeks to resolve diagnostic uncertainties and discriminate between a primary non-response versus azathioprine induced hepatotoxicity.1,3 American guidelines recommend an alternative strategy whereby azathioprine is simultaneously introduced with a lower induction dose of prednisolone.4

In 2018, the United Kingdom Autoimmune Hepatitis (UK-AIH) study (n = 1249) reported significant discrepancies in the care of AIH patients within the National Health Service (NHS).5 The study reported that 55% of patients remained on long-term corticosteroid therapy (treatment lasting longer than 6 months). Moreover, significant treatment variability existed with 29 different corticosteroid and immunosuppression regimens reported.5 Systemic corticosteroids in the treatment of AIH is associated with detrimental effects on quality of life independent of remission status, including negative effects on mobility and ability to perform usual activities.5 In 2019, Van den Brand et al., reported many AIH patients taking long term corticosteroids reported negative effects on their mental health, including depression and chronic fatigue, independent of disease stage.6

With variable corticosteroid and azathioprine regimens resulting in inconsistent management of patients, coupled with the desire to reduce cumulative corticosteroid exposure; the aim of this study was to establish whether earlier introduction of azathioprine facilitated a reduced cumulative corticosteroid burden in AIH patients. Key objectives were to determine the cumulative exposure of corticosteroid in the first 12 months and the maintenance dose over the next five years; timing of azathioprine introduction following commencement of corticosteroids; the dose of azathioprine at introduction and maintenance over a five-year period; number of patients in biochemical remission at 1-, 3- and 5- years from diagnosis; and finally reported rates of corticosteroid associated side effects. Additionally, we wanted to establish if there is an era effect that influenced prednisolone and azathioprine prescribing regimens.

**Methods**

*Study design:*

We performed a retrospective single centre cohort study. Inclusion criteria included patients over 18 years-old diagnosed with AIH between 1970 to 2020 fulfilling the International AIH Group diagnostic criteria (1999 revised criteria and simplified criteria), received induction therapy with prednisone and maintenance therapy with azathioprine.7,8 Exclusion criteria were the inability to determine the exact timing of azathioprine introduction and the corticosteroid withdrawal, presence of overlap syndrome with primary biliary cholangitis or primary sclerosing cholangitis, presence of other liver disease (e.g. viral hepatitis, metabolic dysfunction associated steatotic liver disease, drug induced liver injury), acute severe or fulminant AIH, intolerance to azathioprine or incomplete data.

*Ethics statement*

Ethical approval was deemed not essential according to the National Institute for Health and Care Research (NIHR) assessment tool. The research study was exempted from ethics approval as was deemed a service evaluation by the Hepatology and Pharmacy research and audit group (RAG) at Kings College Hospital (KCH).

*Data collection:*

Patients were identified from our local database of AIH patients. Patient information was gathered from patient medical records. A case report form (CRF) was designed, piloted and revised after extensive comments. The following data were collected: demographics, serology, histology, blood laboratory results and drug treatment regimens. The study specific information regarding patient weight, corticosteroid dose, azathioprine dose and liver biochemistry were collected at time points: 3, 6, 12, 24, 36 and 60 months. As there is no defined time point to starting azathioprine, based on the overall median time to azathioprine commencement in our group, patients were divided arbitrarily into two groups: ‘early’ azathioprine therapy group defined as those who received azathioprine within 8-weeks of corticosteroid initiation and ‘late’ azathioprine group for those who received azathioprine more than 8-weeks after corticosteroid initiation. Biochemical remission was defined as normalisation of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and IgG/globulin levels. 9 Prior to routine IgG monitoring, globulin levels were used as a surrogate marker of biochemical remission. Though suboptimal, clinician-documented patient reported side effects and adverse events were identified retrospectively from patient medical records. Of note, all surviving patients were re-checked for hepatitis C after 1990.

The total cohort was also divided into groups depending on which decade they commenced treatment to establish an era effect. The groups were 1970-1979, 1980-1989, 1990-1999, 2000-2009 and 2010-2020. The prednisolone dose, azathioprine dose and time of introduction and biochemical response were evaluated in each decade.

*Outcomes:*

The primary outcome was the total cumulative exposure of prednisolone at specified intervals over a 5-year follow up period. Secondary outcomes were the number of patients achieving and maintaining biochemical remission over 5-years and corticosteroid related adverse events over a twelve month period. We also evaluated the effect of era on management and outcome of AIH.

*Statistical Analysis:*

Descriptive analysis was conducted across the whole cohort. Statistical analyses were conducted using Graphpad Prism 9 (Graphpad software) and SPSS version 27 (IBM Corporation, Armonk, NY, USA). The Mann-Whitney U test was used for non-parametric continuous variables, one way ANOVA for comparison of more than two groups and Chi‐square test was used to compare categorical data. A p-value <0.05 was considered statistically significant.

**Results**

*Population*

A total of 408 eligible patients with AIH were identified during the entire period of 1970-2020. Of these, 182 patients were excluded because they did not receive classical induction regimens (prednisolone +/-azathioprine) within the first 6 months or due to missing data. The final cohort we present consisted of 226 patients with complete data at all time points (Table 1). One hundred and seventy seven patients (78%) were female, with a median age at diagnosis of 50 years (range 18-82). At diagnosis, 86 (38%) patients presented with cirrhosis. All had biopsy proven AIH.

The median induction dose of prednisolone in all patients were 0.4mg/kg/day (IQR 0.17) (Table 1). The median time to introduction of azathioprine was 8 weeks following commencement of corticosteroid therapy. Median azathioprine dose at initiation was 75mg/day (IQR 25), 0.94mg/kg/day (IQR 0.4) and this dose remained consistent across the five-year follow-up.

*Corticosteroids*

Prednisolone dose and cumulative exposure in the early and late azathioprine groups are described in Table 2. As expected, the prednisolone dose in both groups reduced during the 5-year follow-up. The median prednisolone dose and therefore cumulative prednisolone dose in the early azathioprine group was consistently lower at each time point compared to the late azathioprine group although this did not reach statistical significance.

Of the total cohort, 185 (82%) patients remained on corticosteroid therapy at 12-months, 167 (74%) at 2-years, 147 (65%) at 3-years and 129 (57%) at 5-years. The differences between the two groups are highlighted in Table 1. The number of patients remaining on corticosteroids at the end of 5-year follow-up was higher in the late azathioprine addition group (62%) compared to the early group (52%) but did not reach statistical significance (p=0.33).

*Early azathioprine group*

One hundred and six of 226 (46%) patients started azathioprine within 8 weeks of corticosteroid induction. Of these, 38 (36%) patients started azathioprine concurrently with prednisolone induction therapy; 17 (16%) within 2 weeks of prednisolone induction; 23 (22%) within 4 weeks and the remaining 28 (26%) within 8 weeks of prednisolone induction.

*Late azathioprine group*

One hundred and twenty of 226 (53%) patients comprised the late group who started azathioprine 8-weeks after corticosteroid induction. Of these, 34 (28%) started between 8-12 weeks, 28 (23%) between 13-24 weeks, 24 (20%) between 25-48 weeks and the remaining 34 (28%) started 48 weeks after corticosteroid induction. In the groups who started after 48 weeks of steroid induction, 82% of these were diagnosed between 1970-1990.

*Biochemical remission*

For all patients, the proportion achieving biochemical remission (normal AST/ALT and IgG) from induction therapy was 59.1% at 3-months, 71.7% at 6-months and 82% at 12-months (Table 3). During long term follow-up, 74.2%, 77.8% and 73.6% maintained biochemical remission after 2-, 3- and 5-years respectively.

After 5-years of follow-up, more patients in the early group (76.5%) achieved complete biochemical remission compared to the late group (70.5%) although this did not reach statistical significance (p = 0.44) (Table 3). However, at 6-months, serum ALT level normalised in 80% of patients in the early group compared to 64.5% in the late group (p = 0.01). IgG levels normalised in 68% of the early group compared to 54% in the late group (p = 0.05) at 1-year (Table A in supplementary material)). When stratified per decade, complete biochemical remission was achieved in a greater proportion of patients within the first 6 months of corticosteroid therapy (p = 0.012) in more recent decades (Figure 1). However, this difference was not present from the second year onwards (p = 0.107).

*Corticosteroid related side effects*

Within the first 12 months of commencing corticosteroid therapy, 70% of patients reported experiencing corticosteroid related side effects. The most common reported side effects were hyperglycaemia (19%), Cushing’s syndrome (18%), weight gain (16%) and deterioration of bone health (15%). There was no statistical difference between the early and late group. However, there was a trend towards patients in the late azathioprine group more likely to experience side effects including hyperglycaemia (OR=0.85), weight gain (OR= 0.85), deterioration of bone health (OR=0.83), infection (OR=0.43), visual disturbances (OR=0.47) and fatigue (OR=0.67) compared to the early group (Figure 2).

*Era effect*

We examined the changes in the prednisolone starting dose, duration of exposure and the cumulative dose over five distinct decades; 1970-1979, 1980-1989, 1990-1999, 2000-2009 and 2010-2020. The dose and duration of corticosteroid treatment reduced during each decade (Table 4a). From 6 months of starting corticosteroid treatment, there was a significant difference in the cumulative dose of corticosteroid. At 5-years, the median cumulative dose of corticosteroid in the 1970s was 215.2mg/kg whereas, by 2010 it was 52mg/kg (p <0.001).

The initial starting doses of prednisolone in the 1970’s was 0.33mg/kg/day compared to the 1980s when the dose increased to 0.42mg/kg/day (Table 4b). However, in more recent decades, there was a faster rate of reduction in the corticosteroid dose from the first 6 months of treatment initiation. Most commonly the dose of prednisolone was reduced by 5mg every two weeks. Less patients remained on prednisolone at 1-year, 2-years, 3-years and 5-years in more recent decades, with 88% remaining on corticosteroids at 5-years in the 1970’s reducing to 54% in the most recent decade (p = 0.001) (Figure 3).

Similarly, there was earlier introduction of azathioprine in more recent decades (Figure 3). Azathioprine initiation after corticosteroid induction was 80 weeks during the 1970s, 37 weeks in the 1980s, 33 weeks in 1990s, 13 weeks during the 2000s and 10 weeks from 2010 onwards (p = 0.026). Azathioprine doses did not differ between decades, except for between 2000-2010, where doses were higher at 1.45 mg/kg/day on average from 3 months onwards (Table 4c).

**Discussion**

In this study, we evaluated the timing of thiopurine introduction and its effect on prednisolone exposure in AIH patients. To our knowledge, this study represents the first efforts to examine prescribing practices in AIH over time and we have identified four key findings. Firstly, earlier introduction of azathioprine for the treatment of AIH did not result in a statistically significant reduction in the cumulative dose of prednisolone. Secondly, early introduction of azathioprine initially led to faster normalisation of transaminase but by 12 months, both groups achieved the same rate of biochemical remission. Thirdly, earlier thiopurine introduction was associated with reduction in documented corticosteroid related adverse effects though this was not statistically significant. Lastly, in more recent decades there was a significant reduction in the cumulative exposure to prednisolone with earlier introduction of azathioprine corresponding to a higher rate of biochemical remission within the first year of azathioprine initiation.

In this study, the cumulative prednisolone exposure over 5 years was consistently lower with early azathioprine introduction compared to the late azathioprine initiation, although this was not statistically significant. At 5-years of treatment, a greater proportion of patients remained on corticosteroid therapy in the late group versus the early group though this was also not significant (62% versus 52%, p= 0.33). As well as treatment with azathioprine being refined, steroids remained a mainstay of treatment in this unit. Previous guidelines also incorporated patient symptoms as a preference between high dose prednisone monotherapy versus combination therapy with lower doses of prednisone in combination with azathioprine.10 Thus high dose steroids were given to many patients. Early trials, including the 1973 double- blind prospective trial of prednisone versus azathioprine at our unit showed over a 2 year period, prednisone was superior at improving liver function preventing the development of oesophageal varices and prolonged survival.11 This is similar to the UK-AIH study (n= 1249) which reported that 55% of patients remain on long-term corticosteroid therapy (treatment lasting longer than 6 months).5 A study comparing low dose prednisolone at <0.5mg/kg at induction, to high dose at >0.5mg/kg, showed that patients initiated on high dose prednisolone received a significantly higher cumulative dose of corticosteroid in the first 6 months of treatment (2573mg vs 3870mg, p<0.001).12 This suggests that the starting dose of prednisolone has a greater effect on the cumulative dose of corticosteroid, rather than the time at which azathioprine is initiated. This is important for persons with AIH as some corticosteroid adverse effects are dose related. In our study, the early and late group both had median starting doses of prednisolone at 0.4mg/kg/day.

Late initiation of azathioprine were equally likely to achieve complete biochemical remission at 12 months as well as at 5-years when compared to early azathioprine introduction. However, in the early group, 80% of patients achieved normalisation of AST within 6 months of corticosteroid induction compared to 64.5% in the late group (p= 0.013). In another retrospective study, a rapid reduction in AST level at 8 weeks of treatment was associated with normalisation of transaminase levels in the following year and a lower risk of liver-related death or transplantation compared to patients without a rapid response.13 This suggests that earlier azathioprine introduction may be more favourable in improving long-term outcomes and this warrants further investigation. In addition, our data showed azathioprine was introduced much earlier in recent decades (80 weeks in 1970s compared to 10 weeks in 2010s) with an increase in the proportion of patients achieving complete biochemical remission. Pape et al. also demonstrated that biochemical remission was equally achieved at 12 months in the early azathioprine group (within 2 weeks of corticosteroid induction) and the late group (after 2 weeks) whilst the discontinuation of azathioprine in the first year of treatment was independent of azathioprine initiation timing.14 Although the strategy of delaying introduction of azathioprine in order to avoid hepatotoxicity in the early stages of the disease is described in the EASL guidelines, the evidence is limited.1

Our data showed the documented corticosteroid-related side effects was not significantly different between the early versus late azathioprine initiation. This may be expected given that the cumulative corticosteroid exposure between the 2 groups were not significantly different. However, the likelihood of experiencing infections, visual disturbances, fatigue, deterioration of bone health and hyperglycaemia were higher in the late group compared to the early group (OR = <1). Previous data demonstrated a lower rate of corticosteroid-related side effects in low corticosteroid dose group compared to the high-dose group (18.8% versus 21.3%, p value = 0.56) (10). The retrospective design of our study excluded a detailed assessment because not all adverse events were systematically documented. However, larger observational studies in rheumatoid arthritis clearly show a dose-dependent relationship between cumulative glucocorticoid dose and corticosteroid-related adverse events.15,16 This not only includes severe adverse events, such as cardiovascular mortality and cataract, but also self-reported adverse events, such as cushingoid appearance, sleep disturbance, mycosis, leg oedema, acne, weight gain and shortness of breath.15,16 Although we did not confirm these results in our study, it is intuitive to maintain cumulative prednisolone dosage as low as possible to minimise the risk of corticosteroid-related adverse events. Van Den Brand et al. highlighted that even low dose prednisolone (0.1-0.5mg/day) in the long term maintenance treatment of AIH can result in adverse events, with 25% experiencing corticosteroid related adverse events.6

Interestingly, there was a statistically significant reduction in cumulative prednisolone exposure and the maintenance prednisolone dose in mg/kg/day from 6 months onwards as decades progressed from 1970 to 2020 (p < 0.001). However, the induction corticosteroid dose increased in more recent years, which is likely based on current guidelines.1 The initial starting dose of prednisolone in the 1970s was 0.33mg/kg/day which was in keeping with a prospective trial, conducted at the Royal Free Hospital in London, that used 15mg of prednisolone per day.17  Data derived from the Mayo clinic published in 1975 concluded a higher induction dose of predniso(lo)ne at 30mg per day in combination with azathioprine controlled disease activity better. This practice is reflected in our data whereby the initial dose of prednisolone in the 1980s increased to 0.42mg/kg/day.18 The European guidelines published in 2015 recommend 0.5 – 1mg/kg predniso(lo)ne at induction. This is demonstrated in our cohort as between 2010-2020, the median induction dose of prednisolone was 0.48mg/kg/day.1 Importantly, in more recent years, the corticosteroid dose was weaned more rapidly resulting in a lower 5 year cumulative prednisolone burden.

In this report, the median dose of azathioprine was 0.9 mg/kg/day across the whole cohort. European and American clinical practice guidelines recommend a maintenance dose of azathioprine between 1-2mg/kg/day.1,4 In 1995, Johnson et al., demonstrated that patients in biochemical remission for at least one year with prednisolone and azathioprine could maintain remission with a higher dose of azathioprine monotherapy at 2mg/kg/day.2 As pioneers of azathioprine use, our centre has historically monitored patients on a weekly basis in the first months of treatment to promote fast reduction in steroid use and early introduction of azathioprine. Although clinicians have learned how to use azathioprine over time, a recent survey amongst expert hepatologists showed that azathioprine dosing is not often optimised.19 Genetic polymorphisms in the metabolism of azathioprine lead to variation in levels of metabolites which are associated with adverse drug reactions. AIH patients with insufficient response to azathioprine can be optimised through measuring metabolite levels and with the addition of allopurinol.20,21,22,23,24 Azathioprine metabolite testing has been routinely but not systematically, measured since 2007 in this centre. Thiopurine metabolite testing in AIH demonstrated the average dose of azathioprine for patients in remission at 6 months was 1.2mg/kg/day.22 Metabolite testing was associated with increased rate of biochemical remission at 6 months and therefore reduction in corticosteroids dose.22 Metabolite testing in the failure to achieve or loss of biochemical remission group resulted in dose escalation in 26% of patients.22 This suggests individualised azathioprine dosing with metabolite monitoring may also be a key strategy in the optimisation of thiopurine therapy.

This study has some inherent limitations. The retrospective observational design of the study has considerable bias, especially selection, as only patients with complete data were included. In addition, as a large referral centre, patients are often diagnosed at less experienced centres before referral to us and this can explain why 28% of patients commenced azathioprine 2 years after diagnosis. Despite this, there is a consistency in the data with multiple generations of clinicians managing patients over several decades. We focused in this series on patients treated with index presentations at KCH to ensure complete data. In order to increase our sample size, a multicentre approach could be undertaken. In this study, we did not evaluate long-term outcomes in our patients such as time to liver transplantation, liver related mortality and morbidity since our focus was exclusively on early outcomes. This could be further investigated to establish if azathioprine timing determines long-term outcomes.

To conclude, earlier introduction of azathioprine in AIH did not reduce the cumulative prednisolone exposure over a 5-year follow up, however, there was initially a faster rate of normalisation in transaminases. In more recent decades, prednisolone was weaned at a faster rate which reduced the corticosteroid exposure without negatively impacting biochemical remission. With limited treatment options for the management of AIH, adhering to earlier introduction of azathioprine coupled with prompt reduction in corticosteroid provides vital benefits for patients from both an efficacy and safety perspective.

**Tables**

**Table 1**: Baseline characteristics of all patients at time of AIH diagnosis between 1970-2020

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total cohort (n=226) | Early azathioprine initiation  (n=106) | Late azathioprine initiation  (n=120) | *P* value |
| Female gender, n (%) | 177 (78) | 84 (79) | 93 (77) | 0.75 |
| Age at diagnosis y, median (range) | 50 (18-82) | 50 (18-82) | 50 (18-76) | 0.83 |
| Antibody positive, n (%) | 207 (92) | 95 (89.6) | 112 (93.3) | 0.32 |
| AST at diagnosis IU/L, median (IQR) | 725 (898) | 745 (928) | 706 (898) | 0.89 |
| IgG at diagnosis g/L, median (IQR) | 24.9 (16.33) | 24 (15) | 25 (15) | 0.67 |
| Bilirubin at diagnosis umol/L, median (IQR) | 78.5(168) | 78 (178) | 80 (163) | 0.89 |
| Albumin at diagnosis g/L, median (IQR) | 34(9) | 35 (9) | 34 (9) | 0.6 |
| Cirrhosis, n (%) | 86 (38.1) | 39 (37) | 47 (39) | 0.72 |
| Starting prednisolone dose, mg median (IQR) | 30 (20) | 30 (20) | 30 (20) | 0.45 |
| Starting prednisolone dose, mg/kg median (IQR) | 0.4 (0.17) | 0.4 (0.29) | 0.4 (0.19) | 0.6 |
| Number of patients on corticosteroids at 12 months, n (%) | 185 (82) | 86 (81) | 99 (82) | 0.9 |
| Number of patients on corticosteroids at 24 months, n (%) | 167 (74) | 74 (70) | 93 (77) | 0.5 |
| Number of patients on corticosteroids at 36 months, n (%) | 147 (65) | 65 (61) | 82 (68) | 0.5 |
| Number of patients on corticosteroids at 60 months, n (%) | 129 (57) | 55 (52) | 74 (62) | 0.33 |
| Starting azathioprine dose, mg median (IQR) | 75 (25) | 75 (25) | 75 (25) | 0.61 |
| Starting azathioprine dose, mg/kg median (IQR) | 0.94 (0.4) | 0.94 (0.43) | 0.95 (0.46) | 0.42 |

**Table 2:** Prednisolone dose and cumulative exposure over 5-year follow up in patients in the early vs late azathioprine group

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Months** | **Prednisolone dose, mg, median (IQR)** | | | **Cumulative prednisolone exposure, mg/kg, median (IQR)** | | |
| **Early azathioprine initiation (n=106)** | **Late azathioprine initiation (n=120)** | ***P* value** | **Early azathioprine initiation**  **(n=106)** | **Late azathioprine initiation**  **(n=120)** | ***P* value** |
| **3** | 10 (5) | 11.2 (10) | 0.71 | 21.7 (9.79) | 23.9 (12.02) | 0.69 |
| **6** | 7.5 (6) | 10 (7.5) | 0.92 | 34.8 (14.2) | 37.9 (21.33) | 0.35 |
| **12** | 5 (7.5) | 7.5 (7.5) | 0.12 | 51.6 (31.93) | 56.6 (36.76) | 0.5 |
| **24** | 4.5 (10) | 5 (10) | 0.7 | 72.84 (70) | 74.63 (60.5) | 0.99 |
| **36** | 2.5 (7.5) | 5 (10) | 0.11 | 90.2 (96) | 96.5 (115.74) | 0.34 |
| **60** | 0 (5) | 2.5 (7.5) | 0.16 | 107 (110) | 112 (141) | 0.45 |

**Table 3**: Number of patients achieving biochemical remission in the early vs late azathioprine groups over 5-year follow up. Complete biochemical remission defined as normalisation of both AST and IgG.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Normalisation of AST and IgG** | | | |
|  |
| **Months** | **Total**  **(n=226)**  **n (%)** | **Early azathioprine initiation**  **(n=106)**  **n (%)** | **Late azathioprine initiation (n=120)**  **n (%)** | ***P* value** |
| **3** | 91 (59.1) | 47 (61.8) | 44 (56.4) | 0.49 |
| **6** | 114 (71.7) | 57 (74) | 57 (69.5) | 0.52 |
| **12** | 115 (82.0) | 63 (85.1) | 52 (77.6) | 0.25 |
| **24** | 121 (74.2) | 62 (76.5) | 59 (72) | 0.50 |
| **36** | 119 (77.8) | 58 (79.5) | 61 (76.3) | 0.63 |
| **60** | 95 (73.6) | 52 (76.5) | 43 (70.5) | 0.44 |

**Table 4a:** Cumulative prednisolone exposure in all patients per decade between 1970 to 2020

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Months** | **Cumulative prednisolone exposure, mg/kg, median (IQR)** | | | | | | |
|  | **1970s  (n = 42)** | **1980s  (n= 55)** | **1990s  (n = 37)** | **2000s (n = 57)** | **2010s  ( n = 35)** | ***P* value** |
| **3** | 23.5 (9.3) | 22 (10.4) | 24 (10.8) | 23 (12.2) | 21 (7.89) | 0.684 |
| **6** | 41.1 (16.3) | 37 (18.3) | 39 (22) | 34 (19.8) | 29 (8.51) | 0.004 |
| **12** | 69.72 (29.4) | 57 (26.3) | 60 (35) | 43 (27.6) | 39 (22.10) | <0.001 |
| **24** | 128.3 (62.5) | 92 (55.5) | 87 (44.8) | 56 (32.1) | 47 (42.3) | <0.001 |
| **36** | 178.1 (73.9) | 124 (98.2) | 104 (76.8) | 60 (49.9) | 50 (44.4) | <0.001 |
| **60** | 215.2 (99.8) | 134 (120) | 111 (94.3) | 65 (66.72) | 52 (55.35) | <0.001 |

**Table 4b:** Prednisolone dose in all patients per decade between 1970 to 2020

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Months** | **Prednisolone dose, mg/kg/day, median (IQR)** | | | | | | |
|  | **1970s  (n = 42)** | **1980s  (n= 55)** | **1990s  (n = 37)** | **2000s (n = 57)** | **2010s  ( n = 35)** | ***P* value** |
| **0** | 0.33 (0.20) | 0.42 (0.21) | 0.40 (0.22) | 0.48 (0.25) | 0.48 (0.18) | 0.0031 |
| **3** | 0.20 (0.11) | 0.17 (0.10) | 0.19 (0.12) | 0.14 (0.14) | 0.12 (0.11) | <0.001 |
| **6** | 0.19 (0.08) | 0.13 (0.19) | 0.15 (0.11) | 0.07 (0.08) | 0.06 (0.09) | <0.001 |
| **12** | 0.16 (0.07) | 0.12 (0.07) | 0.1 (0.08) | 0.04 (0.07) | 0.03 (0.08) | <0.001 |
| **24** | 0.2 (0.1) | 0.1 (0.1) | 0.06 (0.07) | 0 (0.1) | 0 (0.1) | <0.001 |
| **36** | 0.1 (0.1) | 0.1 (0.1) | 0.04 (0.09) | 0 (0) | 0 (0) | <0.001 |
| **60** | 0.1 (0.1) | 0 (0.1) | 0 (0.07) | 0 (0) | 0 (0) | <0.001 |

**Table 4c:** Azathioprine starting dose (mg/kg) in the first year of induction in all patients per decade between 1970-2020

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Months** | **Azathioprine dose, mg/kg/day, median (IQR)** | | | | | |
|  | **1970s  (n = 42)** | **1980s  (n= 55)** | **1990s  (n = 37)** | **2000s (n = 57)** | **2010s  ( n = 35)** | ***P* value** |
| **0** | 1.07 (0.34) | 1.03 (0.33) | 0.94 (0.49) | 0.81 (0.42) | 0.71 (0.43) | <0.001 |
| **3** | 1.05 (0.44) | 1.05 (0.54) | 1.00 (0.51) | 1.35 (0.46) | 1.1 (0.34) | 0.00003 (\*0.86) |
| **6** | 1.1 (0.40) | 1.1 (0.7) | 1.02 (0.51) | 1.5 (0.50) | 1.1 (0.30) | <00001 (\*0.81) |
| **12** | 1.1 (0.4) | 1.1 (0.8) | 1.17 (0.68) | 1.5 (0.5) | 1.1 (0.30) | 0.00013  (\*0.211) |

\*P value if 2000s data removed

**Figures**

**Figure 1**: Percentage of patents achieving biochemical remission at 6 months from corticosteroid induction per decade between 1970-2020, p = 0.012

**Figure 2**: Forest plot of odds ratio of corticosteroid related side effects in the early vs late azathioprine groups.

**Figure 3:** Percentage of patients remaining on corticosteroids per decade between 1970 to 2020 at time points 12, 24, 36, 60 months. The difference between the number of patients remaining on corticosteroid therapy at each time point per decade is statistically significant, p = 0.001. Time in weeks from corticosteroid induction to starting azathioprine in all patients per decade between 1970-2020, p = 0.026.

**References**

[dataset] [1] EASL Clinical Practice Guidelines: Autoimmune hepatitis. Journal of Hepatology [Internet]. 2015 Oct;63(4):971–1004. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168827815004584

[dataset]  [2] Johnson PJ, McFarlane IG, Williams R. Azathioprine for Long-Term Maintenance of Remission in Autoimmune Hepatitis. New England Journal of Medicine [Internet]. 1995 Oct 12;333(15):958–63. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199510123331502

[dataset] [3] Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut [Internet]. 2011 Dec 1;60(12):1611–29. Available from: https://gut.bmj.com/lookup/doi/10.1136/gut.2010.235259

 [dataset] [4] Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. Hepatology [Internet]. 2020 Aug 12;72(2):671–722. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/hep.31065>

[dataset] [5] Dyson JK, Wong LL, Bigirumurame T, Hirschfield GM, Kendrick S, Oo YH, et al. Inequity of care provision and outcome disparity in autoimmune hepatitis in the United Kingdom. Alimentary Pharmacology & Therapeutics [Internet]. 2018 Nov;48(9):951–60. Available from: http://doi.wiley.com/10.1111/apt.14968

[dataset] [6] Van den Brand FF, van der Veen KS, Lissenberg-Witte BI, de Boer YS, van Hoek B, Drenth JPH, et al. Adverse events related to low dose corticosteroids in autoimmune hepatitis. Alimentary Pharmacology and Therapeutics. 2019 Nov 1;50(10):1120–6.

[dataset] [7]  Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. Journal of Hepatology. 1999 Nov;31(5).

[dataset] [8] Hennes EM, Zeniya M, Czaja AlbertJ, Parés A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008 Jul;48(1).

[dataset] [9] Pape S, Snijders RJALM, Gevers TJG, Chazouilleres O, Dalekos GN, Hirschfield GM, Lenzi M, Trauner M, Manns MP, Vierling JM, Montano-Loza AJ, Lohse AW, Schramm C, Drenth JPH, Heneghan MA; International Autoimmune Hepatitis Group (IAIHG) collaborators(‡). Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. J Hepatol. 2022 Apr;76(4):841-849.

[dataset] [10] Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM; American Association for the Study of Liver Diseases. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010 Jun;51(6):2193-213. doi: 10.1002/hep.23584. PMID: 20513004.

[dataset] [11] Murray-Lyon, IM, Stern, RB, Williams, R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. Lancet 1973;1:735-737

[dataset][12] Pape S, Gevers TJG, Belias M, Mustafajev IF, Vrolijk JM, van Hoek B, et al. Predniso(lo)ne Dosage and Chance of Remission in Patients With Autoimmune Hepatitis. Clinical Gastroenterology and Hepatology. 2019 Sep 1;17(10):2068-2075.e2.

[dataset][13] Pape S, Gevers TJG, Vrolijk JM, van Hoek B, Bouma G, van Nieuwkerk CMJ, et al. Rapid Response to Treatment of Autoimmune Hepatitis Associated With Remission at 6 and 12 Months. Clinical Gastroenterology and Hepatology. 2020 Jun;18(7).

[dataset][14] Pape S, Gevers TJG, Vrolijk JM, Hoek B, Bouma G, Nieuwkerk CMJ, et al. High discontinuation rate of azathioprine in autoimmune hepatitis, independent of time of treatment initiation. Liver International [Internet]. 2020 Sep 11;40(9):2164–71. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/liv.14513>

[dataset] [15] Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. Annals of the Rheumatic Diseases. 2009 Jul 1;68(7).

[dataset] [16] Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis & Rheumatism. 2006 Jun 15;55(3).

[dataset] [17]G. C. Cook, Rosemary Mulligan, Sheila Sherlock, Controlled Prospective Trial Of Corticosteroid Therapy In Active Chronic Hepatitis, Qjm: An International Journal Of Medicine, Volume 40, Issue 2, April 1971, Pages 159–185

[dataset] [18] W. H. J. Summerskill, Melvyn G. Korman, Helmut V. Ammon and Archie H. Baggenstoss. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared., Gut, 1975, 16, 876-883

[dataset] [19] Liberal R, de Boer YS, Andrade RJ, Bouma G, Dalekos GN, Floreani A, et al. Expert clinical management of autoimmune hepatitis in the real world. Alimentary Pharmacology & Therapeutics. 2017 Mar;45(5).

   [dataset] [20] Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis & Rheumatism. 2006 Jun 15;55(3).

[dataset] [21] Weltzsch JP, Bartel CF, Waldmann M, Renné T, Schulze S. Optimizing thiopurine therapy in autoimmune hepatitis: A multi-center study on monitoring metabolite profiles and co-therapy with allopurinol. Hepatology. 2024;80:S316.

[dataset] [22]  Candels LS, Rahim M, Yeoman A, Wong GW, Heneghan M. Utility of thiopurine metabolite testing in autoimmune hepatitis: defining an optimal therapeutic range for disease management and measurement may avert relapse and adverse drug reactions. Journal of Hepatology. 2020 Aug;73.

[dataset] [23] De Boer YS, van Gerven NMF, de Boer NKH, Mulder CJJ, Bouma G, van Nieuwkerk CMJ. Allopurinol safely and effectively optimises thiopurine metabolites in patients with autoimmune hepatitis. Alimentary Pharmacology & Therapeutics. 2013 Mar;37(6).

[dataset] [24]  L.S. Candels, M.N. Rahim, S. Shah, M.A. Heneghan. Towards personalised medicine in autoimmune hepatitis: measurement of thiopurine metabolites results in higher biochemical response rates. J Hepatol, 75 (2021), pp. 324-332