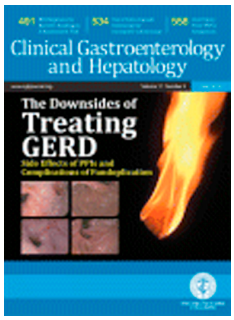
Accepted Manuscript



Predniso(lo)ne Dosage and Chance of Remission in Patients With Autoimmune Hepatitis

Simon Pape, Tom J.G. Gevers, Michail Belias, Ilyas F. Mustafajev, Jan Maarten Vrolijk, Bart van Hoek, Gerd Bouma, Carin M.J. van Nieuwkerk, Johannes Hartl, Christoph Schramm, Ansgar W. Lohse, Richard Taubert, Elmar Jaeckel, Michael P. Manns, Maria Papp, Felix Stickel, Michael A. Heneghan, Joost P.H. Drenth

PII: S1542-3565(19)30008-4
DOI: https://doi.org/10.1016/j.cgh.2018.12.035
Reference: YJCGH 56270

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 23 December 2018

Predniso(lo)ne Dosage and Chance of Remission in Patients With Autoimmune Hepatitis

Simon Pape[1], Tom J.G. Gevers[1], Michail Belias[2], Ilyas F. Mustafajev[1], Jan Maarten Vrolijk[3], Bart van Hoek[4], Gerd Bouma[5], Carin M.J. van Nieuwkerk[5], Johannes Hartl[5], Christoph Schramm[6, 7], Ansgar W. Lohse[6], Richard Taubert[8], Elmar Jaeckel[8], Michael P. Manns[8], Maria Papp[9], Felix Stickel[10], Michael A. Heneghan[11], Joost P.H. Drenth[1]

1. Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands.
2. Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands.
3. Department of Gastroenterology and Hepatology, Rijnstate hospital, Arnhem, The Netherlands
4. Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands.
5. Department of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands.
6. 1st Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
7. Martin Zeitz Centre for Rare Diseases, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany.
8. Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany.
9. Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary.
10. Department of Gastroenterology and Hepatology, University Hospital of Zurich, Zurich, Switzerland.
11. Institute of Liver Studies, King's College Hospital, London, United Kingdom.

Corresponding author:

Joost PH Drenth, MD, PhD

Radboud University Medical Center

Dept. of Gastroenterology and Hepatology

Internal postal code 455

P.O. Box 9101

6500 HB Nijmegen

The Netherlands

Telephone: +31-24-3616999

Fax: +31-24-3635129

joostphdrenth@cs.com

Grant support: SP was supported by a unrestricted grant of FALK Pharma. MP was supported by the Janos Bolyai Research Scholarship of the Hungarian Academy of Sciences (BO/00232/17/5) and the New National Excellence Program of the Ministry of Human Capacities (ÚNKP-18-4 Bolyai Plus).

Disclosures: No potential conflicts that are relevant to the manuscript.

Author contributions:

JD had the original idea and supervised the study. TG supervised the study. SP, IM, JV, BH, GB, CS, CN, AL, RT, EJ, MM, MH, MP and FS provided and collected data. SP, TG and MB analyzed the data. SP wrote the manuscript. All authors critically reviewed the manuscript and approved the final version of the manuscript.

Tables and figures: 6 (+7 as supplementary material)

52 **Word count**

53 Abstract: 260

54 Total manuscript (incl. table/figure legends and references): 3998

Abstract

Background & Aims

Patients with autoimmune hepatitis (AIH) commonly receive induction therapy with predniso(lo)ne followed by maintenance therapy with azathioprine. European Association for Study of the Liver clinical practice guidelines advise a predniso(lo)ne dose range of 0.50–1 mg/kg/day, which leaves room for practice variation. We performed a multicenter study to determine the efficacy of different dose ranges of predniso(lo)ne induction therapy in a large European cohort of patients with AIH.

Methods

We performed a retrospective cohort study using a comparative effectiveness design. We collected data from 451 adults with AIH who began treatment from 1978 through 2017 at 9 centers in 5 European countries. We assigned patients to a high-dose group (initial predniso(lo)ne dose ≥0.50 mg/kg/day; n=281) or a low-dose group (<0.50 mg/kg/day; n=170). Logistic regression was performed to determine difference in outcomes between the groups. The primary outcome was normal serum levels of transaminases at 6 months after initiation of therapy.

Results

There was no significant difference in rates of normalization of transaminases between the high-dose predniso(lo)ne group and the low-dose group (70.5% vs 64.7%; *P*=.20). After multivariable logistic regression with correction for confounders, there was no difference in the likelihood of normalization of transaminases between the groups (odds ratio, 1.21; 95% CI, 0.78 – 1.87; *P*=.38). Patients given an initial high dose of predniso(lo)ne received more predniso(lo)ne over time than patients

started on a lower dose (median doses over 6 months: 3780 mg vs 2573 mg) (*P*<.01).

Conclusions

In a retrospective study of patients with AIH in Europe, we found that the dose of predniso(lo)ne to induce remission in patients with AIH is less relevant than assumed. An initial predniso(lo)ne dose below 0.50 mg/kg/day substantially decreases unnecessary exposure to predniso(lo)ne in patients with AIH.

Keywords

EASL guidelines, ALT, AST, IgG, corticosteroid, induction therapy, cirrhosis, prednisone, prednisolone.

LIST OF ABBREVATIONS

AASLD	American Association for the Study of Liver Diseases
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANA	Anti-nuclear antibody
AIH	Autoimmune hepatitis
CI	Confidence interval
EASL	European Association for the Study of the Liver
IAIHG	International Autoimmune Hepatitis Group
IgG	Immunoglobulin G
INR	International normalized ratio
IRB	Institutional Review Board
LKM1	Liver kidney microsome type 1
OR	Odds ratio
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
SMA	Smooth muscle antibody
SLA/LP	Soluble liver antigen / liver pancreas
ULN	Upper limit of normal

INTRODUCTION

Autoimmune hepatitis (AIH) is a rare, chronic liver disease characterized by inflammatory liver histology, circulating autoantibodies and increased serum levels of immunoglobulin G (IgG). The etiology of AIH is elusive but there is a clear genetic susceptibility [1]. When left untreated, AIH may progress to cirrhosis and end-stage liver disease [2]. Therapy, immunosuppressive by nature, is aimed at inducing and maintaining remission of disease and prevention of fibrosis progression. Biochemical remission, which is defined as normalization of both serum transaminases and serum IgG has been accepted as a surrogate endpoint for treatment [3].

Current therapy for AIH consists of prednisone/prednisolone monotherapy or a combination therapy of predniso(lo)ne and azathioprine. The supporting evidence comes from clinical trials performed in the 1970s and 1980s [4-9]. These studies established the role of predniso(lo)ne in AIH but fail to provide data on its therapeutic window. Predicting the response to predniso(lo)ne treatment is relevant, particularly in AIH, because attenuation of hepatic inflammation reduces the risk of liver related complications in patients with and without cirrhosis [6-8, 10, 11]. However, the role of predniso(lo)ne in patients presenting with acute severe AIH (AS-AIH) is not fully elucidated [12-14]. Regarding the predniso(lo)ne at start of therapy, guidelines provide conflicting recommendations. The American Association for the Study of Liver Diseases (AASLD) and British Society of Gastroenterology (BSG) advise 30 mg/day in combination with azathioprine, which corresponds to 0.50 mg/kg/day in a 60 kg patient [15] [16]. In contrast, the most recent guideline, the European Association for Study of the Liver (EASL) Clinical Practice Guideline suggests a predniso(lo)ne starting dose in a range from 0.50 – 1 mg/kg/day [3]. Furthermore, data on predniso(lo)ne starting dosages in patients with cirrhosis at presentation, are lacking.

In view of these divergent recommendations, practice variation among physicians and centers may arise when it comes to predniso(lo)ne dosages used for AIH induction therapy. Indeed, in a recent International Autoimmune Hepatitis Group (IAIHG) survey among AIH experts, participants reported a dose ranging from 20 to 100 mg/day when asked for the optimal starting dose for a hypothetical 75 kg patient with acute AIH [17, 18]. The lowest effective dose of predniso(lo)ne in AIH and information on a dose-effect relation between predniso(lo)ne and achieved biochemical remission are unclear. Therefore, we established a cohort with AIH patients derived from multiple international centers to compare the efficacy of a high- versus a low-dose predniso(lo)ne induction therapy on biochemical endpoints and steroid-related side effects.

METHODS

Study design

We performed a retrospective cohort study using a comparative effectiveness design. We analyzed AIH patients from nine different centers across five European countries in Europe. Treatment was initiated between 1978 and 2017. Inclusion criteria were a new diagnosis of probable or definite AIH using clinical, biochemical, serological and histopathological results consistent with the simplified or revised IAIHG criteria [19, 20], age ≥18 years at time of diagnosis and induction therapy with predniso(lo)ne. Patients were excluded if they had overlapping features of primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC), suffered from other liver diseases (e.g. viral hepatitis or non-alcoholic fatty liver disease) or had missing endpoint data. Patients who died or underwent liver transplantation before the

primary endpoint, were also excluded. Ethics approval was waived after review by local Institutional Review Board.

Data collection

We collected demographic variables, patient characteristics, serological, histological, laboratory and treatment variables from patient records and local databases. Laboratory values and predniso(lo)ne dosages were collected at baseline and after 1, 2, 3, 6, and 12 months of therapy. Original patient data, including histopathology reports, were used to calculate an AIH diagnostic score for each patient [19-21]. Cumulative predniso(lo)ne dose was calculated using the mean daily predniso(lo)ne dose each month and then adding up the cumulative dosage per month to calculate a cumulative dose over time. Data collection was done using a pre-defined electronic case report form and stored in an online database (Castor Electronic Data Capture, CIWIT B.V., Amsterdam, The Netherlands).

Outcomes

Our primary outcome was normalization of serum transaminases after 6 months of treatment. We used the upper limit of normal (ULN) from each participating center to define normalization of transaminases. Secondary endpoints included biochemical remission (defined as normal serum transaminases and normal serum IgG), normalization of transaminases at 52 weeks, occurrence of steroid-related side effects: diabetes mellitus requiring anti-diabetic medication, hypertension requiring anti-hypertensives and osteopenia and osteoporosis confirmed by bone densitometry.

Analysis

We used the starting dose predniso(lo)ne of 0.50 mg/kg/day as advised in the EASL Clinical Practice Guideline as cut-off point to distinguish the high and low dose predniso(lo)ne group [3]. The low dose group consisted of patients who received a predniso(lo)ne starting dose of <0.50 mg/kg/day, and the high-dose group were patients treated with ≥0.50 mg/kg/day. Univariate comparisons of baseline characteristics between the two groups were made using chi-square, Mann-Whitney U test or t-test as appropriate. We defined acute severe AS-AIH as a presentation with an international normalized ratio (INR) ≥1.5 without histological evidence of cirrhosis [12].

In order to determine the differences in remission between the two groups we performed logistic regression with normalization of transaminases as dependent variable. With this method we were able to adjust the primary outcome for potential confounders. We pre-defined a set of potential confounders (institute, cirrhosis, AS-AIH, age, year of diagnosis, use of maintenance therapy) based on an assumed association with the primary outcome. Furthermore, significant baseline differences between groups were included as confounders in the model. All potential confounders were added to the final regression model. Because of the high proportion of missing IgG serum levels after 6 months, we performed a sensitivity analysis with biochemical remission as dependent variable, this is defined as normal serum transaminases and normal IgG, which is the definition according to the EASL Clinical Practice Guideline [3]. In addition, we performed a subgroup analysis and tested for possible effect modification in patients with cirrhosis at baseline and AS-AIH by adding interaction terms (treatment group x variable) in the main model. Results of multivariable logistic regression are given as odds ratios (ORs) and 95% confidence intervals (CI). We performed an additional multivariable logistic

regression analysis to produce institute-specific ORs and consequently a summary OR for the primary outcome. Heterogeneity among effect sizes was assessed using the I^2 index. An I^2 index $\geq$50% was used to indicate medium-to-high heterogeneity

In addition, we used propensity score matching to compare matched groups of patients based on baseline disease activity. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics. We included biomarkers of disease activity (baseline serum transaminases, bilirubin), use of maintenance therapy, gender and cirrhosis to calculate a propensity score with treatment group (high vs. low dose predniso(lo)ne) as dependent variable. Patients were matched 1:1 using nearest neighbor matching without replacement. P-values <0.05 were considered statistically significant. Statistical analysis was done with SPSS version 25 (IBM Corporation, Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Missing data

We used a multiple imputation model as the primary method to account for missing data in baseline AST and ALT values. Twenty imputed datasets were generated using predictive mean matching. Pooled odds ratio's (OR) from the imputed datasets were used as final result.

RESULTS

Population characteristics

A total of 880 patients with an established AIH diagnosis were evaluated for this study. Eventually, 451 patients could be included in our analysis. Main reasons for exclusion were missing endpoint data and variant syndromes with PBC and PSC (figure 1). A total of 281 (62.3%) patients were treated with high-dose predniso(lo)ne

(≥0.50 mg/kg/day) and 170 (37.7%) patients were treated with low-dose predniso(lo)ne (<0.50 mg/kg/day). Baseline characteristics of the study population are summarized in table 1. There was a large variation in initial predniso(lo)ne dosages that were prescribed (supplementary figure 2). Patients in the high-dose group had significantly higher transaminases and bilirubin at presentation, although IgG did not differ between the groups. Cirrhosis at index biopsy was present in 25.9% of the patients in the low-dose group, compared to 15.3% in the high-dose group ($p < 0.01$). Forty-seven (10.4%) patients presented with acute-severe AIH (AS-AIH) and were equally distributed between the two arms.

Most of the patients received maintenance therapy (80.2% high-dose group vs. 83.5% low-dose group, $p = 0.39$) during their first six months of treatment. Maintenance therapy consisted mainly of azathioprine (table 2). Other maintenance therapies included 6-mercaptopurine (3.5%), 6-tioguanine (1.6%), mycofenolate mofetil (3.1%) and tacrolimus (1.3%). Most patients were still using predniso(lo)ne at 6 months of treatment (87.4% of patients in the high-dose group vs. 83.5% of patients in the low-dose group ($p = 0.32$)) and a majority of patients was on a prednisone dose ≤10 mg at six months (53.2% high dose vs. 58.2% low dose, $p = 0.33$). Median time to a prednisone dose ≤10 mg was 24 weeks in both groups ($p = 0.06$). The median cumulative predniso(lo)ne dose of patients with high dose of predniso(lo)ne was higher (3780 mg) than of those who started on a low dose (2573 mg, $p < 0.01$).

Treatment response: high vs. low dose predniso(lo)ne

In the high-dose group, 64.7% of patients achieved normalization of transaminases at six months of treatment compared to 70.5% of patients in the low-

dose group. However, this result was not significant (p = 0.20). Looking at biochemical remission, incorporating normal IgG at 6 months in patients with available IgG (268 patients: 86 patients in the low-dose group, 182 patients in the high-dose group), remission rates remained similar between the two groups: 63.7% of patients were in remission in the high-dose group compared to 60.5% of patients in the low-dose group (p = 0.61) (table 3, figure 2). After one year of treatment the majority of patients in both groups reached normalization of transaminases (76.2% of patients in the high dose group vs. 77.6% of patients in the low dose group, p = 0.77, data available for 357 patients). When dividing the patients up into quintiles according to initial predniso(lo)ne dose, we found that patients with a median initial predniso(lo)ne dose of 0.31 mg/kg/day still reached normalization of transaminases at six months in 62.2% of the cases (supplementary figure 1). Cumulative predniso(lo)ne dose over 6 months and initial predniso(lo)ne dose between patients with and without normalization of transaminases did not reach the level of statistical difference (3290 mg vs. 3395 mg, p = 0.40; 0.27 mg/kg/day vs. 0.30 mg/kg/day, p = 0.29). There was no difference in initial starting dose and rates of normalization of transaminases between patients who received monotherapy predniso(lo)ne (n = 62) compared to patients who received combination therapy (n = 389) (0.58 mg/kg/day vs. 0.55 mg/kg/day, p = 0.50; 61.3% vs. 69.4%; p = 0.20).

Treatment response: multivariable analysis

In a multivariable logistic regression model we did not find a significant difference in chance on normalization of transaminases between the high- and low-dose predniso(lo)ne group. When adjusted for institute, age, gender, ALT and AST at baseline, year of diagnosis, cirrhosis, use of maintenance therapy and AS-AIH, the OR for normalization of transaminases for patients who were treated with a high dose

of predniso(lo)ne was 1.21 (95% CI 0.78 – 1.87, p = 0.38). Of all covariates in the model, only cirrhosis was significant (p = 0.04). We performed a second analysis, using institute-specific adjusted ORs to calculate a pooled summary OR. With this method, the OR for normalization of transaminases was 1.21 (0.67 – 2.19). Heterogeneity between institutes was low (I^2 = 0%) (supplementary figure 3).

The adjusted OR for biochemical remission (n = 268) for patients who were treated with a high dose of predniso(lo)ne was 1.05 (95% CI 0.59 – 1.86, p = 0.88). The adjusted OR for normalization of transaminases after one year of treatment was 0.87 (95% CI 0.50 – 1.50, p = 0.61).

Treatment response after propensity score matching

Using propensity score matching we established two matched groups of 108 patients each in the high and low dose predniso(lo)ne groups with equally distributed disease activity scores. There were no differences in rates of normalization of transaminases (73.1% vs. 66.7%, p = 0.30) and biochemical remission (62.0% vs. 68.5%, p = 0.45) between high and low dose patients, respectively (table 4).

Treatment response in patients with cirrhosis

Eighty-six patients (19.1%) presented with cirrhosis at baseline. Compared to non-cirrhotics, patients with cirrhosis were more likely to be men (p = 0.01) and had lower transaminases at presentation (supplementary table 1). Overall, normalization of transaminases at six months was lower in patients with cirrhosis vs. non-cirrhotics (58.1% vs. 70.7%, p = 0.03). Rates between cirrhotics and non-cirrhotics did not differ in the low dose group (61.4% vs. 65.9%, p = 0.59), but in the high dose group there was a significant advantage for non-cirrhotic patients (54.8% vs. 73.2%, p = 0.02). There was no interaction between cirrhosis and treatment group (p value for

interaction = 0.52). The adjusted OR for normalization of transaminases for patients with cirrhosis treated with a high dose of predniso(lo)ne was 0.96 (0.35 – 2.63, p = 0.93).

Treatment response in AS-AIH

Our cohort consisted of 47 patients who presented with AS-AIH (supplementary table 2). Most patients were treated with a high dose of predniso(lo)ne. Rates of normalization of transaminases for AS-AIH patients treated with a high dose predniso(lo)ne were higher when compared to patients treated with a low dose of predniso(lo)ne, although not statistically significant (75.9% vs. 61.1%, p = 0.28). There was no interaction between AS-AIH and treatment group (p value for interaction = 0.45). The adjusted OR for normalization of transaminases for AS-AIH treated with a high dose of predniso(lo)ne was 1.50 (0.34 – 6.61, p = 0.59).

Steroid related side effects

Percentage steroid related side effects (diabetes, osteopenia, osteoporosis, hypertension) did not differ between the low and high dose predniso(lo)ne groups: 18.8% of patients in the low dose group experienced steroid related side effects during the first year of therapy compared to 21.3% of patients in the high dose group (p = 0.56). Focusing on each individual steroid related adverse effect, steroid-induced diabetes and osteoporosis occurred more frequent in the high dose group, but this did not meet the level of statistical significance (supplementary table 4).

DISCUSSION

AIH patients who receive low dose predniso(lo)ne as induction therapy (<0.50 mg/kg/day) are just as likely to achieve normalization of transaminases and biochemical remission as patients treated with higher doses of predniso(lo)ne (≥0.50

mg/kg/day). The cumulative predniso(lo)ne burden over time was substantially lower in the <0.50 mg/kg/day group during the first 6 months of therapy (2573 mg versus 3870 mg), although this difference did not result in reduction of steroid related side effects.

There are no randomized controlled trials that compare various starting doses predniso(lo)ne in AIH. A recent cohort study compared two different predniso(lo)ne regimens in 71 AIH patients coming from a single center [22]. A group with an initial 30 mg/day predniso(lo)ne dose (0.48 mg/kg) with fast tapering towards 10 mg was compared with a group that received 40 mg/day (0.62 mg/kg) as initial dose with a slower tapering regimen. The fast tapering group had lower remission rates compared to the slow tapering group, but the difference was not statistically significant (59.4% vs. 79.5%, p = 0.065). We did not observe such a difference between remission rates between the high and low dose group. Fast tapering of predniso(lo)ne might result in lower remission rates, however, we were not able to investigate this in our study.

A logical consequence of higher starting dose is that the cumulative predniso(lo)ne dosages will likely be higher. Indeed, we found that the exposure to predniso(lo)ne in the high treatment group was 47% higher. This did not translate to a higher incidence of adverse events. The retrospective design of our study may have precluded a detailed assessment as not all adverse events were systematically documented. Large observational studies in rheumatoid arthritis clearly show a dose dependent relation between cumulative glucocorticoid dose and steroid-related adverse events. This holds for severe adverse events such as cardiovascular mortality and cataract, but also for self-reported adverse events as cushingoid appearance, sleep disturbance, mycosis, leg edema, acne, weight gain and

shortness of breath [23-25]. Although we did not confirm these results in our AIH population, it is intuitive to keep cumulative predniso(lo)ne dosage as low as possible to minimize the risk of steroid-related adverse events.

Eighty-six (19.1%) patients had cirrhosis at presentation, which is in line with earlier published series [26-28]. Cirrhotics had lower baseline ALT, AST and IgG serum levels, which accords with previous reports [10]. Cirrhotics were more likely to receive a lower dose of predniso(lo)ne (0.49 mg/kg/day vs. 0.60 mg/kg/day for non-cirrhotics). It is possible that physicians are reluctant to prescribe higher doses of predniso(lo)ne in cirrhotic patients due to the increased risk of infections associated with glucocorticoid therapy [29]. However, our study shows that lower predniso(lo)ne dosing in cirrhosis does not impair efficacy when compared to higher dosing (61.4% vs. 54.8%).

Our study comes with a number of limitations. Firstly, due to its retrospective nature, this study is subject to confounding by indication and selection bias. Only cases with enough data points were included for our analyses and we had to exclude a substantial number of patients due to missing data. However, this is the largest multicenter AIH cohort to date with accurate data during the first six months of treatment, which allows extrapolation to real world practice. Furthermore, despite the fact that biochemical disease activity was dissimilar between the two treatment groups, we managed to provide data on a subset of patients with comparable biochemical disease activity which showed no difference in rates of normalization of transaminases or biochemical remission. Secondly, we used normalization of transaminases as primary endpoint. The recent EASL Clinical Practice Guideline states that normalization of IgG should be taken into account when defining biochemical remission of AIH [3]. However, we found that IgG as outcome measure is

not part of routine laboratory testing in all institutions at 6 months after start of induction therapy, which resulted in a high number of missing IgG data points. We performed a sensitivity analysis for patients with an available IgG at six months, which showed no different results than our primary analysis. Although histological remission is the desired endpoint for every AIH patient, routine liver biopsies in AIH are not clinical practice and biochemical remission has been accepted as surrogate endpoint for histological remission in AIH. This is supported by a recent study which confirmed that biochemical remission predicts remission of histological disease activity and even regression of fibrosis [30]. Thirdly, we did not collect data on liver transplantation, liver related mortality and morbidity so we are not able to make any projections about the long-term outcomes of our patients.

Our study established that there is appreciable practice variation among physicians who treat AIH patients: more than one-third of our cohort was treated with initial predniso(lo)ne dosages lower than recommended by the EASL Clinical Practice Guideline [3]. Based on our results, we suggest to use an initial starting dose of <0.50 mg/kg/day in AIH, since this will prevent unnecessary exposure to high cumulative doses of predniso(lo)ne with potential severe side effects while retaining efficacy.

In conclusion: the predniso(lo)ne dosage to induce remission in patients with AIH is less relevant than hitherto assumed. We found that remission was achieved in the majority of cases regardless of predniso(lo)ne dosage. The important ramification of our study is that the advised predniso(lo)ne dosages range may be lowered without attenuating efficacy.

REFERENCES

1. van Gerven NM, de Boer YS, Zwiers A, et al. HLA-DRB1*03:01 and HLA-DRB1*04:01 modify the presentation and outcome in autoimmune hepatitis type-1. Genes Immun 2015;16:247-52.
2. Krawitt EL. Autoimmune hepatitis. N Engl J Med 2006;354:54-66.
3. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015.
4. Lamers MM, van Oijen MG, Pronk M, et al. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. J Hepatol 2010;53:191-8.
5. Soloway RD, Summerskill WH, Baggenstoss AH, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. Gastroenterology 1972;63:820-33.
6. Kirk AP, Jain S, Pocock S, et al. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. Gut 1980;21:78-83.
7. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N Engl J Med 1995;333:958-63.
8. Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. Lancet 1973;1:735-7.
9. Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Q J Med 1971;40:159-85.
10. Landeira G, Morise S, Fassio E, et al. Effect of cirrhosis at baseline on the outcome of type 1 autoimmune hepatitis. Ann Hepatol 2012;11:100-6.
11. Feld JJ, Dinh H, Arenovich T, et al. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. Hepatology 2005;42:53-62.
12. Yeoman AD, Westbrook RH, Zen Y, et al. Prognosis of acute severe autoimmune hepatitis (AS-AIH): the role of corticosteroids in modifying outcome. J Hepatol 2014;61:876-82.
13. De Martin E, Coilly A, Ichai P, et al. The role of corticosteroids in acute-severe autoimmune hepatitis is still highly debatable. J Hepatol 2015.
14. Moenne-Loccoz R, Severac F, Baumert TF, et al. Usefulness of corticosteroids as first-line therapy in patients with acute severe autoimmune hepatitis. J Hepatol 2016;65:444-6.
15. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51:2193-213.
16. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut 2011;60:1611-29.
17. Liberal R, de Boer YS, Andrade RJ, et al. Expert clinical management of autoimmune hepatitis in the real world. Aliment Pharmacol Ther 2017;45:723-732.
18. de Boer YS, Liberal R, Vergani D, et al. Real-world management of juvenile autoimmune liver disease. United European Gastroenterol J 2018;6:1032-1038.
19. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169-76.
20. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-38.

21. Wobser H, Paur T, Schnoy E, et al. Suitability of the simplified autoimmune hepatitis score for the diagnosis of autoimmune hepatitis in a German cohort. United European Gastroenterol J 2018;6:247-254.
22. Purnak T, Efe C, Kav T, et al. Treatment Response and Outcome with Two Different Prednisolone Regimens in Autoimmune Hepatitis. Dig Dis Sci 2017;62:2900-2907.
23. del Rincon I, Battafarano DF, Restrepo JF, et al. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol 2014;66:264-72.
24. Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 2006;55:420-6.
25. Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis 2009;68:1119-24.
26. Werner M, Prytz H, Ohlsson B, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol 2008;43:1232-40.
27. van Gerven NM, Verwer BJ, Witte BI, et al. Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands. Scand J Gastroenterol 2014;49:1245-54.
28. Muratori P, Granito A, Quarneti C, et al. Autoimmune hepatitis in Italy: the Bologna experience. J Hepatol 2009;50:1210-8.
29. Dixon WG, Kezouh A, Bernatsky S, et al. The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case-control study. Ann Rheum Dis 2011;70:956-60.
30. Hartl J, Ehlken H, Sebode M, et al. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. J Hepatol 2017.

Tables & Figures

Table 1:

	< 0.50 mg/kg/day (n = 170)	≥ 0.50 mg/kg/day (n = 281)	*P* value
Female sex, n (%)	125 (73.5%)	213 (75.8%)	0.59
Age at diagnosis, year (SD)	52.03 (15.35)	49.67 (17.47)	0.13
Simplified IAIHG score, median	6	7	<0.01
ALT x ULN, median (IQR)*	7.12 (12.69)	13.44 (21.00)	<0.01
AST x ULN, median (IQR)†	8.52 (17.40)	13.48 (24.27)	<0.01
Bilirubin (µmol/l), median (IQR)‡	29 (83)	48 (177)	0.01
IgG (g/l), median (IQR)¶	20.79 (10.90)	21.60 (13.00)	0.10
Cirrhosis, n (%)	44 (25.9%)	42 (14.9%)	<0.01
AS-AIH, n (%)	18 (10.6%)	29 (10.3%)	0.93

Baseline characteristics of the study population at time of AIH diagnosis. ALT, alanine aminotransferase; AS-AIH, acute-severe autoimmune hepatitis; AST, aspartate aminotransferase; IAIHG, International Autoimmune Hepatitis Group; IgG, immunoglobulin G, IQR: interquartile range; SD, standard deviation; ULN, upper limit of normal. * Available for 369 patients. † Available for 449 patients. ‡ Available for 434 patients. ¶ Available for 381 patients

Table 2:

	< 0.50 mg/kg/day (n = 170)	≥ 0.50 mg/kg/day (n = 281)	*P* value
Predniso(lo)ne dose at start (mg/kg/day), median (IQR)	0.38 (0.15)	0.73 (0.32)	<0.01
Predniso(lo)ne dose at start (mg/day), median (IQR)	30 (11)	50 (20)	<0.01
On predniso(lo)ne at 6 months, n (%)*	146 (87.4%)	237 (90.5%)	0.32
Predniso(lo)ne dose ≤10 mg at 6 months, n (%)*	85 (58.2%)	126 (53.2%)	0.33
Predniso(lo)ne dose at 6 months (mg/kg/day), median (IQR)	0.08 (0.09)	0.10 (0.11)	<0.01
Predniso(lo)ne dose at 6 months (mg/day), median (IQR)	7.5 (5.0)	7.5 (5.0)	0.07
Cumulative predniso(lo)ne dose over 6 months (mg), median (IQR)	2573 (1470)	3780 (2450)	<0.01
Predniso(lo)ne dose per day (mg/kg/day), median (IQR)	0.20 (0.09)	0.33 (0.20)	<0.01
On maintenance therapy at 6 months, n (%) †	134 (80.2%)	222 (83.5%)	0.39
AZA, n (%)	118 (88.1%)	192 (86.5%)	0.67
6-MP, n (%)	6 (4.5%)	10 (4.5%)	0.99
6-TG, n (%)	4 (3.0%)	3 (1.4%)	0.28
MMF, n (%)	3 (2.2%)	11 (5.0%)	0.20
TAC, n (%)	1 (0.7%)	2 (0.9%)	0.88
Other, n (%)	2 (1.5%)	4 (1.8%)	0.83

Treatment characteristics of the study population. 6-MP, 6-mercaptopurine; 6-TG, 6-tioguanine; AZA, azathioprine; IQR, interquartile range; MMF, mycophenolate mofetil; TAC, tacrolimus. * Available for 383 patients † Available for 433 patients

Table 3:

	<0.50 mg/kg/day (n = 170)	≥0.50 mg/kg/day (n = 281)	*P* value
Normalization of transaminases at 6 months	110 (64.7%)	198 (70.5%)	0.20
	<0.50 mg/kg/day (n = 86)	≥0.50 mg/kg/day (n = 182)	*P* value
Biochemical remission at 6 months	52 (60.5%)	116 (63.7%)	0.61

Primary outcome per treatment group. Primary outcome was normalization of serum transaminases (ALT/AST) after six months of therapy. A sensitivity analysis for biochemical remission was done in patients with available IgG at six months. Biochemical remission is defined as normalization of transaminases and IgG. ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G.

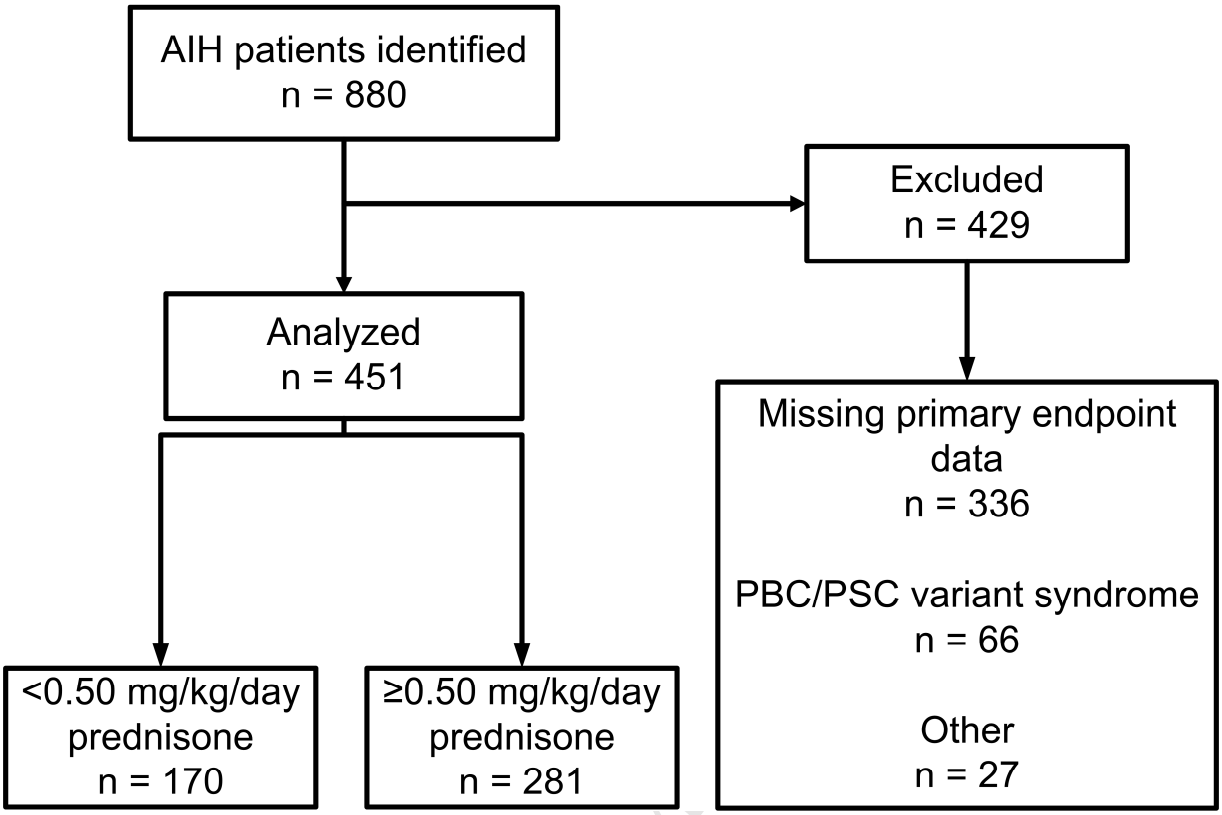
Table 4

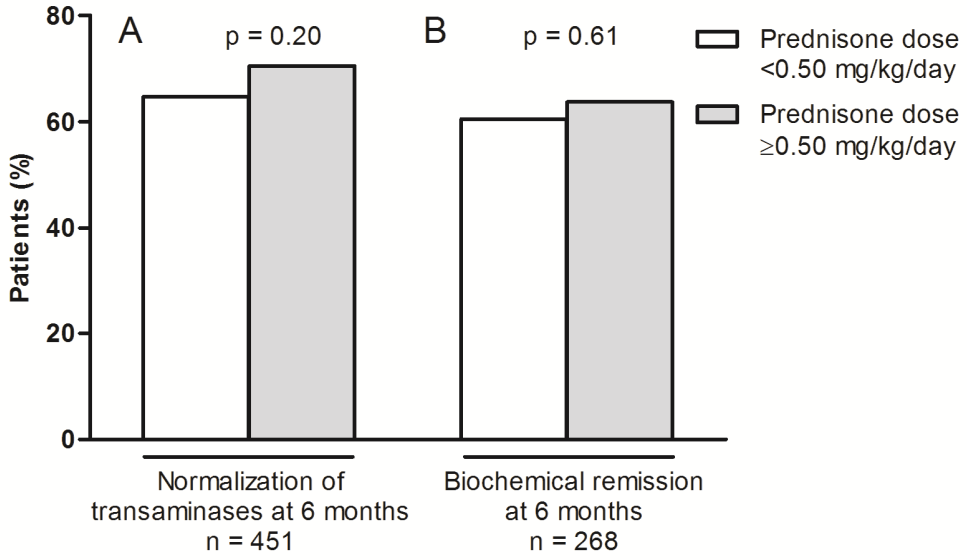
	< 0.50 mg/kg/day (n = 108)	≥ 0.50 mg/kg/day (n = 108)	*P* value
Female sex, n (%)	83 (76.9%)	82 (75.9%)	0.87
Age at diagnosis, year (SD)	52.04 (16.13)	50.79 (17.73)	0.59
Predniso(lo)ne dose at start (mg/kg), median (IQR)	0.39 (0.15)	0.69 (0.32)	<0.01
ALT x ULN, median (IQR)	6.77 (12.89)	7.44 (15.64)	0.28
AST x ULN, median (IQR)	7.86 (16.30)	8.35 (19.85)	0.58
Bilirubin (µmol/l), median (IQR)	24.40 (56.7)	34.80 (173.5)	0.10
IgG (g/l), median (IQR)	20.40 (10.50)	20.80 (15.70)	0.26
Cirrhosis, n (%)	13 (12.0%)	15 (13.9%)	0.69
Use of maintenance therapy	93 (86.1%)	90 (83.3%)	0.57
Normalization of transaminases at 6 months, n (%)	72 (66.7%)	79 (73.1%)	0.30
Biochemical remission at 6 months, n (%)*	37 (68.5%)	44 (62.0%)	0.45

Baseline characteristics and outcomes after propensity score matching. A propensity score was calculated using baseline transaminases, bilirubin, cirrhosis, gender and use of maintenance therapy. The matched cohort consists of 216 patients. ALT, alanine aminotransferase; IQR, interquartile range; SD, standard deviation. * Available for 125 patients

Fig 1. Flowchart of all AIH patients included in this study. PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

Fig. 2. Primary outcome per treatment group. A: Rates of normalization of serum transaminases. B: Rates of biochemical remission, defined as normalization of serum transaminases and serum IgG. IgG, immunoglobulin G.





Background

Guidelines advise a predniso(lo)ne range (0.50–1 mg/kg/day). We performed a multicenter study to determine the efficacy of different doses of predniso(lo)ne induction therapy in a large European cohort of patients with AIH.

Findings

There was no difference in the likelihood of normalization of transaminases between patients given an initial high vs. a low dose of predniso(lo)ne. Patients who began therapy on a higher dose received more predniso(lo)ne over time than patients started on a lower dose.

Implications for patient care

The dose of predniso(lo)ne given as induction therapy for patients with AIH is less relevant than assumed. An initial predniso(lo)ne dose below 0.50 mg/kg/day substantially decreases unnecessary exposure to predniso(lo)ne in patients with AIH.

Supplementary material belonging to:

Prednisone dosage and chance of remission in patients with autoimmune hepatitis: an international multicenter cohort study

Simon Pape[1], Tom JG Gevers[1], Michail Belias[2], Ilyas F Mustafajev[1], Jan Maarten Vrolijk[3], Bart van Hoek[4], Gerd Bouma[5], Carin MJ van Nieuwkerk[5], Johannes Hartl[5], Christoph Schramm[6, 7], Ansgar W Lohse[6], Richard Taubert[8], Elmar Jaeckel[8], Michael P Manns[8], Maria Papp[9], Felix Stickel[10], Michael A Heneghan[11], Joost PH Drenth[1]

Table of contents:

Supplementary table 1: Characteristics of patients with cirrhosis at presentation

	Cirrhosis N = 86	No Cirrhosis N = 365	*P* value
Female sex, n (%)	55 (64%)	283 (77.5%)	0.01
Age at diagnosis, year (SD)	52.58 (17.97)	50.08 (16.41)	0.21
Prednisone dose at start (mg/kg), median (IQR)	0.49 (0.41)	0.60 (0.37)	0.01
ALT x ULN, median (IQR)*	6.87 (9.99)	12.46 (21.15)	<0.01
AST x ULN, median (IQR)†	7.25 (14.07)	12.52 (23.68)	<0.01
Bilirubin (µmol/l), median (IQR)	39.50 (80.50)	40 (168.30)	0.78
IgG (g/l), median (IQR)	20.67 (10.90)	23.60 (16.70)	<0.01
Normal transaminases at six months, n (%)	50 (58.1%)	258 (70.7%)	0.03
<0.50 mg/kg/day	27/44 (61.4%)	83/126 (65.9%)	0.59
≥0.50 mg/kg/day	23/42 (54.8%)	175/239 (73.2%)	0.02

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G; IQR, interquartile range; ULN, upper limit of normal. * Available for 369 patients. † Available for 449 patients.

Supplementary table 2: Characteristics of patients who presented with acute-severe AIH

	AS-AIH N = 47	Normal AIH N = 404	*P* value
Female sex, n (%)	30 (63.8%)	308 (76.2%)	0.06
Age at diagnosis, year (SD)	47.00 (17.80)	50.97 (16.57)	0.12
Prednisone dose at start (mg/kg), median (IQR)	0.60 (0.41)	0.57 (0.39)	0.74
ALT x ULN, median (IQR)*	23.12 (25.67)	8.63 (18.39)	<0.01
AST x ULN, median (IQR)†	19.46 (24.93)	10.07 (20.77)	<0.01
Bilirubin (µmol/l), median (IQR)‡	193 (262)	31 (115.6)	<0.01
IgG (g/l), median (IQR)	27.45 (15.50)	20.9 (10.8)	0.02
Normal transaminases at six months, n (%)	33/47 (70.2%)	275/404 (68.1%)	0.77
<0.50 mg/kg/day	11/18 (61.1%)	99/152 (65.1%)	0.74
≥0.50 mg/kg/day	22/29 (75.9%)	176/252 (68.1%)	0.50

AS-AIH is defined as INR ≥ 1.5 at baseline and absence of cirrhosis at index biopsy. ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G; IQR, interquartile range; ULN, upper limit of normal *Available for 369 patients. † Available for 449 patients. ‡ Available for 434 patients.

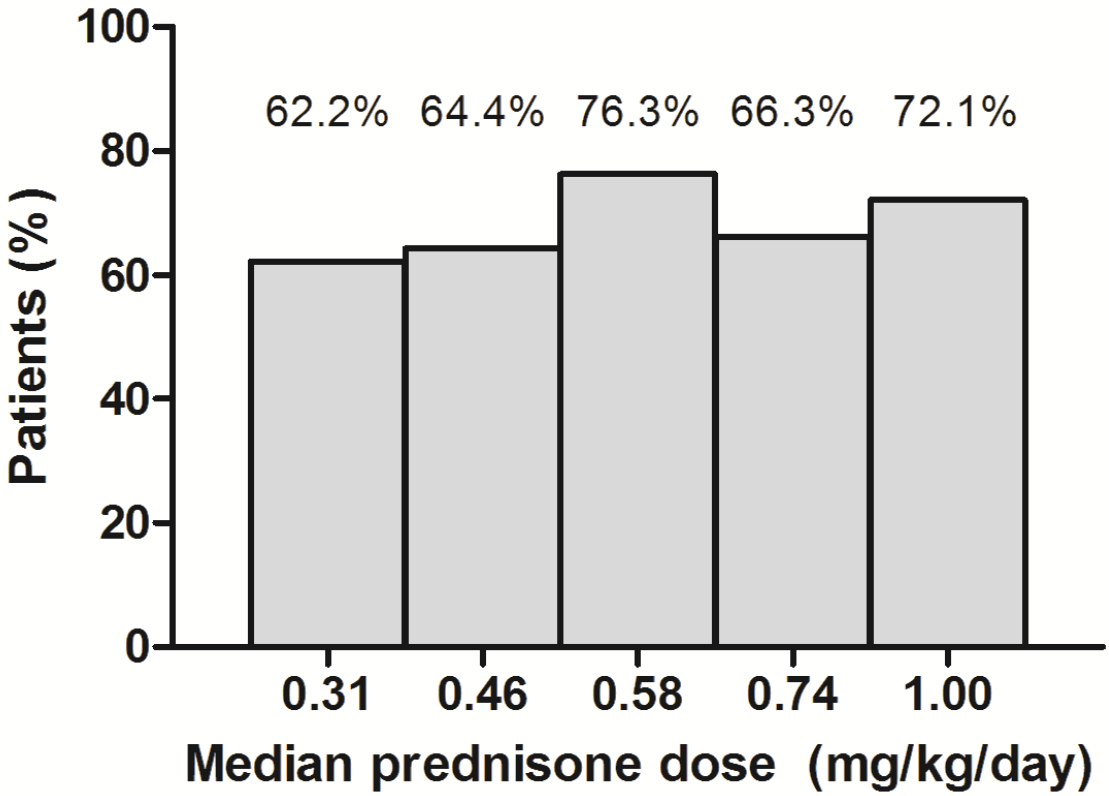
Supplementary table 3: Distribution of patients per institute

	<0.50 mg/kg/day (N = 170)	≥0.50 mg/kg/day (N = 281)
Radboud University Medical Center, The Netherlands	46	24
Rijnstate Hospital, The Netherlands	8	13
Leiden University Medical Center, The Netherlands	19	21
VU University Medical Center, The Netherlands	28	13
University Medical Center Hamburg-Eppendorf, Germany	15	86
King's College Hospital, United Kingdom	46	45
Hannover Medical School, Germany	2	50
University of Debrecen, Hungary	4	18
University Hospital of Zurich, Switzerland	2	11

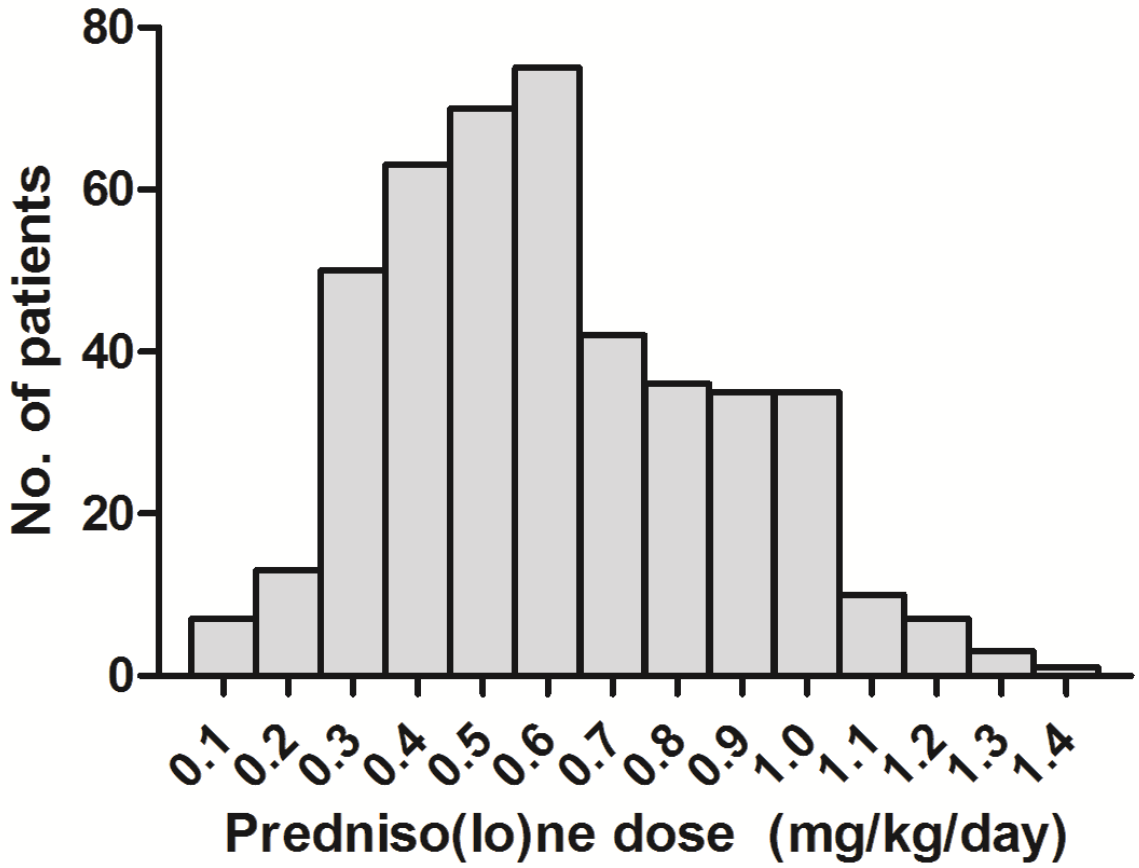
Supplementary table 4

Steroid related side effects	<0.50 mg/kg/day (n = 154)	≥0.50 mg/kg/day (n = 235)	*P* value
Total	29 (18.8%)	50 (21.3%)	0.56
Diabetes	6 (3.9%)	18 (7.7%)	0.13
Osteopenia	14 (9.1%)	13 (5.5%)	0.18
Osteoporosis	4 (2.6%)	15 (6.4%)	0.09
Hypertension	5 (3.2%)	5 (2.1%)	0.50

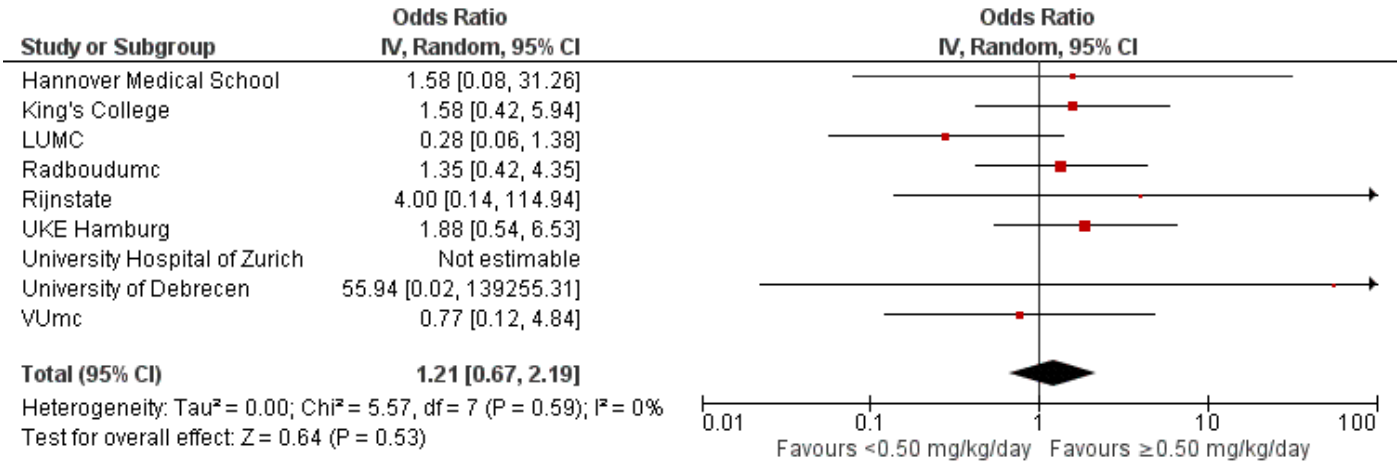
Occurrence of steroid-related side effects per treatment group. Data available for 389 patients. One patient experienced two events in the ≥0.50 mg/kg/day group



Supplementary figure 1. Rates of normalization of transaminases in AIH in different treatment groups. Patients were divided into five groups of equal size (quintiles) based on initial prednisone dose. Normalization rates per median initial prednisone dose are displayed. Sample size per group: 0.31 mg/kg/day: n = 90; 0.46 mg/kg/day: n = 90; 0.58 mg/kg/day: n = 93; 0.74 mg/kg/day: n = 92; 1.00 mg/kg/day: n = 86. The difference between rates is not statistically significant (Chi-square, p = 0.23).



Supplementary figure 2. Frequency distribution of initial predniso(lo)ne dosages (mg/kg) used for induction therapy in patients with AIH (n = 451).



Supplementary figure 3. Pooled odds ratio (OR) for the primary outcome (normalization of transaminases at 6 months of therapy) based on ORs per institute. All ORs are adjusted after multivariable logistic regression.