Budesonide as first-line treatment in patients with autoimmune hepatitis seems inferior to standard predni(so)lone administration

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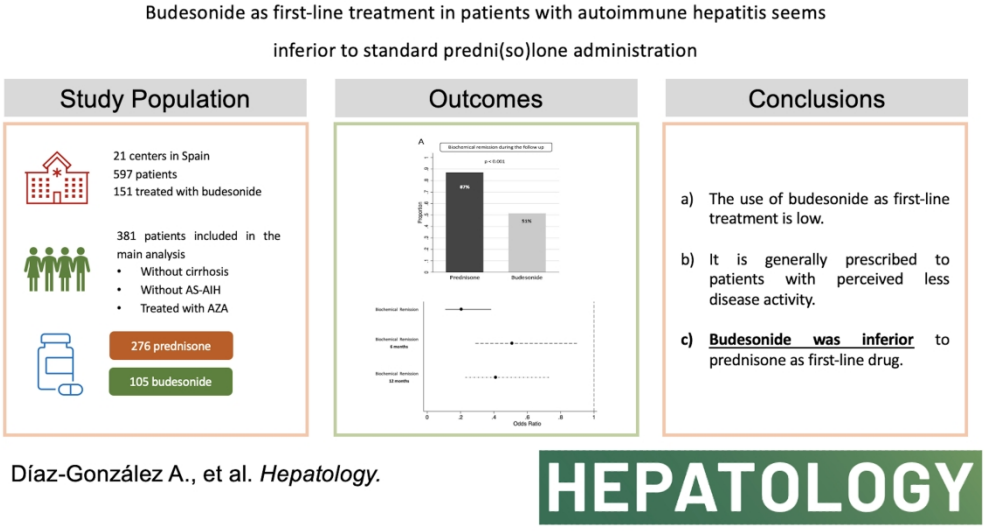

Graphical Abstract

326x178mm (300 x 300 DPI)

Budesonide as first-line treatment in patients with autoimmune hepatitis seems inferior to standard predni(so)lone administration

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List of Abbreviations: AIH: autoimmune hepatitis; IPTW: inverse probability of treatment weighting; PS: propensity score; AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyltranspeptidase; ALP: Alkaline phosphatase; BR: Biochemical response; ULN: Upper limit of normal; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; AZA: Azathioprine; IgG: Immunoglobulin G; AEs: Adverse events; INR: International normalized ratio; ANA: Anti-nuclear antibodies; ASMA: Anti-smooth muscle antibodies; STD: Standardized mean differences; AS-AIH: Acute severe autoimmune hepatitis; OR: odds ratio; CI: Confidence interval; IQR: Interquartile range.

Conflict of interests

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Abstract

Background & Aims: In patients with non-severe acute or chronic autoimmune hepatitis (AIH) without cirrhosis, clinical practice guidelines recommend indistinct use of prednisone or budesonide. However, budesonide is infrequently used in clinical practice. We aimed to describe its use and compare its efficacy and safety with prednisone as first-line options.

Approach & Results: This was a retrospective, multicenter study of 105 naïve AIH patients treated with budesonide as the first-line drug. The control group included 276 patients treated with prednisone. Efficacy was assessed using logistic regression and validated using inverse probability of treatment weighting propensity score (IPTW-PS). The median time to biochemical response (BR) was 3.1 months in patients treated with budesonide and 4.9 months in those with prednisone. The biochemical response rate was significantly higher in patients treated with prednisone (87% vs. 49% of patients with budesonide, p<0.001). The probability of achieving BR, assessed using the IPTW-PS, was significantly lower in the budesonide group (OR 0.20; 95%CI 0.11-0.38) at any time during follow-up, and at 6 (OR 0.51; 95%CI 0.29-0.89) and 12 months after starting treatment (0.41; 95%CI 0.23-0.73). In patients with transaminases <2xULN, BR was similar in both treatment groups. Prednisone treatment was significantly associated with a higher risk of adverse events (24.2% vs. 15.9%, p=0.047).

Conclusions: In the real-life setting, the use of budesonide as first-line treatment is low, and it is generally prescribed to patients with perceived less disease activity. Budesonide was inferior to prednisone as a first-line drug but was associated with fewer side effects.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by the presence of elevated transaminases, hypergammaglobulinemia, autoantibodies and typical histological findings (interface hepatitis, lymphoplasmacytic portal infiltrate) (1). Although AIH was the first liver disease to be targeted with an effective treatment, it is still a challenging condition. In fact, its management has not substantially changed over the last 40 years, consisting of the induction of response with steroids and maintaining this with a steroid-sparing drug, usually azathioprine (AZA) (1,2). In this regard, the European Association for the Study of the Liver (EASL) (1) and the American Association for the Study of Liver Diseases (AASLD) (2) recommend using predniso(lo)ne and AZA as the first therapeutic option in these patients. AASLD guidelines also suggest the use of budesonide with AZA as an alternative agent in patients without cirrhosis or a severe acute presentation (1–3) .

Budesonide is a synthetic corticosteroid with local anti-inflammatory effects and a more favorable safety profile compared to predniso(lo)ne (4). This safer profile is the consequence of lower systemic exposure to the drug, as more than 90% of the drug is eliminated in hepatic first-pass clearance (5,6). Studies published in the 90s evidenced the potential benefit of budesonide in AIH (7). However, it was not until 2005 that a phase II clinical trial showed that budesonide was effective in the induction of response in naïve patients with AIH (8). These results were confirmed in a phase III randomized trial comparing budesonide plus AZA and prednisone plus AZA as first-line treatment (6). In this trial, the authors showed that budesonide was not only effective but was also superior to prednisone in achieving biochemical response in patients with AIH (6).

Nevertheless, the use of budesonide in the real life setting is far from widespread (4), being even avoided in some centers (9). This is probably due to the limited information on the subgroup of patients who may benefit from budesonide treatment. Thus, we aimed to: 1) describe the use of budesonide as a first-line drug in a large cohort of untreated AIH patients, 2) compare its safety and efficacy with prednisone in the real-world clinical practice, and 3) identify the profile of patients who would benefit from budesonide.

Materials and methods

Patients

We performed a retrospective, multicenter cohort study of patients diagnosed with AIH in 21 referral centers in Spain participating in the ColHai (the Spanish Registry for Cholestatic and Autoimmune Liver Diseases) registry. The inclusion criteria were: 1) the diagnosis of AIH using the simplified International Autoimmune Hepatitis Group criteria (score ≥6) always including a liver biopsy (10), 2) 18 years of age or older at diagnosis, and 3) induction therapy with either prednisone or budesonide in combination with AZA. The exclusion criteria were: 1) previous treatment with any immunosuppressive drug, 2) the presence of variant forms of AIH, or 3) any other active liver disease that could interfere with treatment response or evaluation.

For this project, we defined two cohorts: a) the budesonide cohort, including previously untreated patients who received budesonide as the first-line drug, and b) the prednisone cohort, in which naïve patients were treated with prednisone as first-line treatment.

The study was approved by the institutional review board at Marqués de Valdecilla University Hospital (internal code: 2020.275) and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki.

Data collected for the analysis

Data were anonymized and collected from medical records by each local investigator and were centrally compiled and analyzed. In terms of baseline characteristics, we recorded demographic variables, the presence of other medical conditions, including autoimmune and metabolic comorbidities, as well as serologic, histologic, laboratory and treatment parameters. Induction and maintenance drugs and doses were also collected. Finally, evolutionary events and treatment-related adverse events (AEs) were also analyzed.

Definitions

As per guidelines (1,2), biochemical response (BR) was defined as complete normalization of both serum transaminases and immunoglobulin G (IgG). The upper limit of normality (ULN) at each center was used for the definition of transaminases and IgG normalization. Rapid responders were defined as patients who presented a decrease of transaminases of more than 80% 8 weeks after treatment initiation (11). The presence of cirrhosis was recorded at each center according to the typical clinical, ultrasound and histological characteristics (METAVIR stage 4 or Ishak stage 6). Acute severe autoimmune hepatitis (AS-AIH) was defined by the presence of jaundice and significant liver dysfunction evidenced by an international normalized ratio (INR) >1.5 in patients with a time between the onset of symptoms and presentation of less than 26 weeks (12).

Doses

The initial doses of budesonide, prednisone, and AZA were collected from all patients. Dates of dose modification and drug withdrawal were collected when available. Cumulative doses were calculated by multiplying the daily dose of the drug by the number of days in treatment with that dose and then, adding up the cumulative dosage until that time. The equivalence of budesonide to prednisone was calculated according to previous publications and clinical trials in liver diseases (13), assuming that 3 mg of budesonide is equivalent to 10 mg of prednisone.

Endpoints

The primary endpoint was BR at any time, and at 6 and 12 months after starting immunosuppressive treatment. Secondary endpoints were the occurrence of steroid-associated AEs and the use of budesonide as a first-line drug in patients with AIH.

Statistical Analysis

Quantitative variables were expressed as median and interquartile range (IQR, 25th–75th percentiles). Categorical variables were presented as absolute frequencies and percentages (%). An inverse probability of treatment weighting (IPTW) propensity score (PS) method was used to balance the two cohorts (budesonide and prednisone).

The parameters included in the final PS model were: age (years), gender (male vs. female), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), INR, total bilirubin, IgG, the inverse of IgG, IgG squared, the square root of IgG, anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), cirrhosis (yes vs. no), and the inverse of ALT. The balance between baseline parameters of each cohort was assessed, before and after the application of IPTW weights, stabilized by treatment prevalence, and by means of standardized mean differences (STD) (14,15). A STD >20% was considered unbalanced (16). The Fisher's exact test was used to compare categorical variables and for quantitative or ordinal variables we used non-parametric methods: Mann-Whitney (two groups) or Kruskal-Wallis (more than two groups) tests for independent data, and the Wilcoxon signed rank test (two groups) or the Friedman test (more than two groups) for dependent data. Logistic regression was used to determine associations between treatment and clinical characteristics. Results of the univariable and multivariable logistic regression are presented as odds ratio (OR) and 95% confidence interval (CI).

The level of significance was set at 5% (two-sided). IPTW analyses were performed using SAS V.9.4 software (SAS Institute, Cary, North Carolina, USA). All other analyses and statistical tests were performed using Stata Statistical Software: Release 14.1. College Station, TX: StataCorp LLC).

Results

Baseline characteristics

Twenty-one centers from the ColHai registry treating 2763 patients with AIH participated in the study. One hundred fifty-one patients (5.4%) receiving budesonide as the first-line drug between 2009 and 2020 were enrolled in the study (budesonide cohort). In addition, 446 patients treated with prednisone at these centers were included as the control group (prednisone cohort). Controls were selected to match the same year of the diagnosis of AIH. Considering that budesonide is not recommended for patients with cirrhosis or those with AS-AIH, we excluded these patients from the present analysis. Patients not receiving AZA were also excluded. Therefore, 381 patients were analyzed, 276 patients treated with prednisone and 105

patients receiving budesonide. The baseline characteristics of the patients included in the study are summarized in Table 1. Briefly, most patients were women (n=268, 70%) with a median age of 61 (IQR 47.8–70.2) and 110 patients (28.9%) presented at least one immune-mediated comorbidity, being autoimmune thyroid diseases (n= 48, 12.6%) the most prevalent. Patients treated with budesonide had statistically significant lower values of AST (128 vs. 642 UI/L), ALT (198 vs. 753 UI/L), ALP (119 vs. 160 UI/L), GGT (98 vs. 176 UI/L), total bilirubin (1 vs. 2.2 mg/dL) and ferritin levels (150 vs. 253 ng/mL). The median budesonide, prednisone, and AZA starting doses were 9 mg (IQR 9 – 9), 50 mg (IQR 30 – 60), and 50 mg (IQR 50 – 50), respectively. As shown in Table 1, there were no significant differences in the cumulative doses of corticosteroids and AZA at 6 and 12 months.

Budesonide was completely withdrawn in 34 (32%) and 62 (59%) patients at 6 and 12 months, respectively. At 6 months, 22 (65%) patients had stopped budesonide after achieving BR, 8 (24%) due to lack of response, 1 (2%) due to AEs, and in 3 (9%) cases by patients' decision. At 12 months, 43 (69%) patients discontinued budesonide after achieving BR, 12 (19%) due to lack of response, 2 (3%) due to AEs, and the remaining cases (5%) by patient's decision. Prednisone was withdrawn in 58 (21%) and 95 (34%) patients at 6 and 12 months of starting treatment, respectively. At 6 months, the drug was discontinued in 50 (86%) patients after achieving BR, 5 (9%) as consequence of AEs and 3 (5%) by patients' decision. At 12 months, 84 (88%) stopped prednisone after achieving BR, 6 (7%) due to AEs and 5 (5%) in the context of patient's decision. Differences in drug withdrawal rate at both timepoints were $p = 0.057$ at 6 months and $p < 0.001$ at 12 months.

Biochemical response

After a median follow-up period of 5.6 years (IQR 3.2 - 8.9), complete BR was documented in 294 (77%) patients. The median time to BR was 4.4 months (IQR 2.1 – 8.8). In the prednisone cohort, 240 (87%) patients achieved BR during follow-up (Figure 1a), with a median time to BR of 4.9 months (IQR 2.2 – 9.3). BR at 6 and 12 months after starting immunosuppressive treatment was attained in 143 (52%) and 199 (72%) patients, respectively (Figure 1b-c). In the budesonide cohort, BR was achieved in 54 (51%) patients during follow-up (Figure 1a), with a median time to BR of

3.1 months (IQR 1.5 – 6.9). At 6 and 12 months of treatment, BR was documented in 39 (37%) and 51 (49%) patients, respectively (Figure 1b-c). The median values of transaminases, IgG and doses at 6, 12 months and last follow-up according to the presence or absence of BR are shown in Supplementary Table 1. The occurrence of BR was significantly higher in patients treated with prednisone at any time during follow-up (p<0.001), at 6 (p=0.010) and 12 months (p<0.001).

The probability of achieving BR was also significantly higher in the prednisone group at 6 months (OR 0.54; 95% CI 0.34 – 0.87), at 12 months (OR 0.36; 95% CI 0.23 - 0.58) and during the follow-up (0.16; 95% CI 0.09 - 0.27). Figure 2 shows the Kaplan-Meier curve with the probability of achieving BR during follow-up. Variables with a p value <0.1 in the univariate analysis were included the multivariate analysis using a stepwise logistic regression model. As ferritin >2.1 x ULN and IgG <1.9 x ULN have been described as predictive factors of treatment response (2), they were also included in the model. Treatment with prednisone (vs. budesonide) and ferritin levels > 2.1 x ULN were independently associated with the probability of BR at 6 months (OR 0.16; 95% CI 0.05-0.47), and at 12 months (OR 0.29; 95% CI 0.10 – 0.82). At any time during follow-up both prednisone treatment (vs. budesonide, OR 0.15; 95% CI 0.07 – 0.33) and IgG <1.9 x ULN (OR 0.35; 95% CI 0.15 – 0.86) were significantly associated with a higher probability of BR (Supplementary Table 2).

Finally, for a more accurate evaluation of the impact of treatment in achieving BR and to minimize the potential selection bias, an IPTW-PS was performed. After the application of IPTW the cohort was adequately balanced for comparisons between groups. The pre- and post- IPTW STD are summarized in Supplementary Table 3. Patients treated with budesonide presented a lower probability of achieving BR at any point during follow-up with an OR of 0.20 (95% CI 0.11 – 0.38; p<0.001), and at 6 (OR 0.51; 95% CI 0.29-0.89; p=0.019) and 12 months (OR 0.41; 95% CI 0.23 – 0.73; p=0.003) (Figure 3).

Biochemical remission in the entire cohort

Considering that this work is based on real-life clinical practice, the probability of achieving BR with prednisone and budesonide was also evaluated in the whole cohort

(n=597) including patients with cirrhosis, AS-AIH and without AZA treatment. The baseline characteristics of cohort are shown in Supplementary Table 4.

During the follow-up, 465 patients (77.9%) achieved BR. In the budesonide group, 57 patients (37.7%), 75 patients (49.7%) and 80 patients (53%) achieved remission at 6 and 12 months and during follow-up, respectively. In patients treated with prednisone, biochemical remission was achieved in 217 (48.7%), 301 (67.5%) and 385 (86.3%) at 6 and 12 months and during follow-up.

After the application of the IPTW-PS, and once balance was adequate (Supplementary Table 3), patients treated with budesonide also presented a lower probability of achieving BR at any point during follow-up with an OR of 0.25 (95% CI 0.14-0.46; p<0.001) and at 12 months (OR 0.51; 95% CI 0.29-0.90; p=0.022) after starting treatment (Supplementary Figure 1). We also identified a trend towards a lower probability of BR at 6 months a (OR 0.64; 95% CI 0.36-1.19; p=0.166).

Besides steroid treatment, no other baseline characteristic was associated with BR at 6 or at 12 months. Nevertheless, rapid responders measured by rapid ALT decline or combined rapid AST plus ALT decline presented a higher probability of achieving BR both at 6 and 12 months of treatment (Supplementary Table 5). When this analysis was performed in both cohorts separately, rapid response was also strongly associated with the probability of BR in patients treated with prednisone, but not in those receiving budesonide (Supplementary Table 6).

Profile of patients who will benefit from budesonide ~~Biochemical response in the budesonide cohort~~

Finally, we wanted to identify the subgroup of patients with AIH in whom budesonide obtained a similar BR rate as compared to prednisone. We found that in patients with low baseline transaminases, BR rates were similar between the budesonide and prednisone cohorts. Indeed, in patients with transaminase levels ≤2 x ULN, the BR rates were 71.4% in the budesonide cohort and 70.6% in the prednisone cohort (p=0.942). In addition, lower GGT values at baseline, were significantly associated with a higher rate of BR (p=0.015) (Table 2).

Adverse events

Steroid-related AEs were documented in 113 (22%) patients, appearing in 91 (24.2%) patients treated with prednisone and in 22 (15.9%) patients treated with budesonide (p=0.047). These differences vanished when patients with cirrhosis were excluded from the analysis, showing a similar incidence of AEs in both groups (p=0.119).

In terms of specific AEs, only the presence of osteoporosis was significantly higher in the prednisone group (Table 3). However, this increased risk was also associated with age, as patients older than 60 years had a significantly higher risk of osteoporosis (OR 5.19 (95% CI 1.15-23.4)). The presence of cirrhosis did not significantly increase the risk of osteoporosis. The development of AEs was not associated with the cumulative doses of prednisone or budesonide (p = 0.697).

DISCUSSION

This study evaluated the effectiveness of budesonide in a real-life scenario and found that this drug was not as effective as prednisone. AIH patients treated with budesonide had a lower probability of achieving BR than those treated with prednisone as the first-line drug. The incidence of BR was steadily superior in the prednisone group not only during follow-up but also at 6 and 12 months. Only patients with transaminase levels < 2 x ULN had similar BR when treated with budesonide or prednisone.

Although clinical practice guidelines recommend budesonide as an adequate alternative to prednisone, its use is far from widespread. In fact, the use of budesonide as either a first- or second-line drug is low as reported in several studies (17). A recently published survey evaluating real-life clinical management of AIH in 33 centers around the world showed that budesonide was not the induction therapy in any case (9), emphasizing the perceived marginal usage of this drug. Consistent with these data, in the present study we show that budesonide is far from being the preferred drug, as it was only indicated in 5.4% of patients newly diagnosed with AIH. Budesonide-treated patients were significantly different from those receiving prednisone, reinforcing the preconceived idea that budesonide is reserved for a particular subgroup of patients. In fact, budesonide was mainly employed in patients with low

baseline transaminases, suggesting that this drug is preferred in patients with less severe disease.

The efficacy of budesonide was demonstrated in a randomized clinical trial published in 2010 comparing the two drugs in adults with AIH (6). This study showed that budesonide was an effective drug in this scenario (6) and led to the recommendation of the use of budesonide as an alternative to prednisone by international clinical practice guidelines (1,2). Interestingly, this trial also showed that budesonide was not only effective, but also superior to prednisone. While 47% of patients treated with budesonide reached the primary endpoint of the study, only 18.4% of patients treated with prednisone did so. The explanation for these unexpected results probably lies in the design of the trial and the definition of the primary endpoint. In fact, this endpoint included not only the achievement of BR but also reaching it in the absence of steroid-related AEs. However, this unconventional endpoint was also used in a similar trial carried out in a pediatric AIH population(18). Nonetheless, the results were notably different: the primary endpoint was only achieved in 16% and 15% of patients treated with budesonide and prednisone, respectively, without identifying statistically differences between the two treatment arms(18). In addition, it is important to highlight that prednisone induction doses in the former trial(6) were lower than the prednisone doses used in the current study. To clarify the potential influence of dosage on outcomes, we recorded not only the initial doses used in each patient but also the cumulative doses of both drugs. We found that the cumulative doses at 6 and 12 months were similar in both cohorts (p=0.529 and p=0.994, respectively) and were not associated with the probability of achieving BR. Therefore, we consider that the differences in initial doses did not influence the results. It is important to note that, to compare cumulative corticosteroid doses, we assumed that 9 mg of budesonide were equivalent to 30 mg of prednisone. This was the equivalence employed in the randomized clinical trial evaluating the efficacy of budesonide in AIH(6). However, the actual equivalence between these two drugs is not completely clear and a few studies conducted in patients with inflammatory bowel disease suggested that 9 mg of budesonide were clinically equivalent to 40 mg of prednisone(19).

Beyond these trials, the body of evidence is scarce (20–22). In fact, the small amount of information available includes a very limited number of patients treated with

budesonide, many of whom were diagnosed with variant syndromes, and in some cases the definition of biochemical response did not conform to what is recommended by the current international guidelines.

Unlike these studies, which were underpowered for obtaining robust information and conclusions, our work was endowed with a larger number of patients from many different referral centers, overcoming potential single-center limitations. Moreover, once the differential profile of patients according to drug choice had been identified, the design of the IPTW analysis allowed direct comparison between groups after achieving an appropriate balance. As mentioned above, patients treated with budesonide were less likely to achieve BR than those treated with prednisone. However, these results should not be taken as an indication of a lack of efficacy of the drug. Forty-nine percent of patients treated with budesonide reached BR during follow-up, which is similar to that reported in the original trials. In fact, we found that patients with transaminases levels below 2-fold ULN at diagnosis had a similar probability of achieving BR as patients treated with prednisone.

After having documented the inferiority of budesonide with respect to prednisone, we wanted to identify predictive factors that may determine higher odds of reaching BR. Besides the treatment, we did not identify any other baseline factor with predictive capacity. In this scenario, an evolutionary event has recently been shown to predict BR. The results of a large multicenter European study showed that patients treated with prednisone who presented a reduction of AST $\geq$ 80% after 8 weeks on treatment -rapid responders-, had a higher probability of achieving BR at 6 and at 12 months after treatment initiation(11). In our cohort we identified that rapid responders had a greater likelihood of BR at 6 and at 12 months. Although Pape *et al*.(11) showed that this predictive ability was related to a rapid AST decline, we identified that ALT as well as the combined reduction of both AST plus ALT, but not AST alone, were related to a higher probability of BR at these timepoints. Notwithstanding, when stratified by treatment arms, this prediction ability persisted only in the prednisone cohort (not in budesonide treated patients).

Regarding the development of AEs, we identified differences between the two groups: patients treated with prednisone had a higher incidence of AEs. However, when patients with cirrhosis were excluded, the emergence of toxicities was not significantly

different between the two groups. These results suggest that the stage of liver fibrosis explains, at least in part, the higher risk of AEs observed in patients treated with prednisone. We did not identify differences in the appearance of severe AEs, except for osteoporosis. Nevertheless, we found that the emergence of osteoporosis was also related to age, as patients older than 60 years were at higher risk. We did not find any influence of cumulative drug doses on the development of AEs. However, these data should be interpreted with caution because the rate of AEs reported here is lower than that of the former trial. This is probably the consequence of the retrospective study design, as many non-severe steroid-related AEs might not have been registered in the medical records by the treating physicians, leading to underreporting of their appearance. However, a recent Dutch work showed that not only prednisone exposure increased the risk of AEs, but also treatment with budesonide significantly increased the risk of cataracts and bone fractures(4).

Our study is not free of limitations, mostly linked to the retrospective design of the study. Firstly, the choice of induction therapy was at the discretion of each treating physician, lacking predefined criteria for drug choice and leading to the described baseline differences disclosed in the manuscript. Nevertheless, the design of the IPTW analysis helped to overcome this potential limitation. Secondly, the AEs may have been underreported and/or underdiagnosed, as mentioned above. Thirdly, we cannot provide information about the modified hepatitis activity index or liver stiffness, as this information was not available for revision in some centers.

In summary, we identified that the use of budesonide in the real-life setting was low and was associated with a lower probability of achieving BR with respect to prednisone. However, budesonide was associated with a lower rate of AEs. Although we did not identify any baseline predictor of response, a rapid decrease of ALT or ALT plus AST was associated with a higher probability of BR in patients treated with prednisone. Patients with low transaminase levels at diagnosis (< 2 x ULN) had similar BR with both corticosteroid treatments and might benefit from the lower number of AEs associated with budesonide treatment.

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FIGURE LEGENDS

Figure 1: Biochemical response in the prednisone and budesonide cohorts in patients without cirrhosis, without AS-AIH and treated with AZA. Patients treated with prednisone presented significant higher biochemical response rates. **A:** Biochemical response during follow-up. **B:** Biochemical response at 6 months. **C:** Biochemical response at 12 months.

Figure 2: Kaplan-Meier curve with the probability of achieving biochemical remission during follow-up.

Figure 3: Probability of response after the application of the IPTW in patients without cirrhosis, without AS-AIH and treated with AZA. Patients treated with budesonide presented a significantly lower probability of biochemical response.

Supplementary Figure 1: Probability of response after the application of the IPTW in the whole cohort. Patients treated with budesonide presented a significantly lower probability of biochemical response.

Table 1. Baseline characteristics of the cohort after excluding patients with cirrhosis, AS-AIH and those not treated with azathioprine.

	Global cohort (N=381)	Budesonide (N=105)	Prednisone (N=276)	p value
Female sex (n, %)	268 (70.3)	75 (71.4)	193 (69.9)	0.774
Age, years (median, IQR)	61 (47.8 – 70.2)	61,1 (45,9 – 71.3)	60,9 (48,6 – 69,6)	0.889
Other AI disease (n, %)	110 (28.9)	25 (23.8)	85 (30.9)	0.172
AST, IU/L (median, IQR)	403 (118 – 970)	128 (72 – 387)	642 (164 – 1103)	<0.001
ALT, IU/L (median, IQR)	522 (179 – 1202)	198 (109 – 518)	753 (261 – 1361)	<0.001
ALP, IU/L (median, IQR)	148 (104 – 221)	119 (83 – 183)	160 (113 – 244)	<0.001
GGT, IU/L (median, IQR)	151 (71 – 294)	98 (44 – 264)	176 (91 – 308)	<0.001
Bilirubin, mg/dL (median, IQR)	1.6 (0.7 – 5.4)	1 (0.6 – 1.6)	2.2 (0.9 – 7.2)	<0.001
INR (Median, IQR)	1.1 (1 – 1.2)	1 (1 – 1.1)	1.1 (1 – 1.2)	<0.001
Ferritin µg/L (median, IQR) *	201 (79 – 726)	150 (62 – 372)	253 (86 – 860)	<0.001
Ferritin >2.1xULN (n, %) *	69 (28.6)	11 (15.5)	58 (34.1)	<0.001
ANA ≥1/80 (n, %)	288 (77,8)	79 (77.4)	209 (78)	0.912
ASMA ≥1/40 (n, %)	194 (53.1)	50 (51)	144 (53.9)	0.621
IgG mg/dL (median, IQR)	1800 (1390 – 2400)	1713 (1261 – 2358)	1800 (1420 – 2407)	0.152
Interface hepatitis (n, %)^	300 (86.5)	85 (86.7)	215 (86.3)	0.924
Lymphoplasmacytic infiltration (n, %)^	330 (95.1)	94 (95.9)	236 (94.8)	0.658

Biliary Changes (n, %)	47 (13.6)	10 (10.2)	37 (15)	0.238
Simplified AIH score (median, IQR)	6 (6 – 8)	6 (6 – 8)	6 (6 – 8)	0.296
Induction dose (median, IQR)	-	9 (9 – 9)	50 (30 – 60)	-
Cumulative doses at 6 months+ (median, IQR)	3247.9 (2449.7 – 4050)	3517.9 (2449.7 - 4597.9)	3234.1 (2514.4 - 3853.1)	0.529
Cumulative doses at 12 months+ (median, IQR)	4331.8 (3240 – 5670)	4545 (2973.9 – 7065)	4324.297 (3300 - 5352.3)	0.994
Cumulative doses of AZA at 6 months+ (median, IQR)$	9006.25 (9006.2 - 13509.4)	9006.2 (9006.2 -18012.5)	9006.2 (9006.2 - 9006.2)	0.306
Cumulative doses of AZA at 12 months+ (median, IQR)$	18262.5 (18262.5 - 27393.75)	18262.5 (18262.5 - 36525)	18262.5 (18262.5 - 18262.5)	0.306

*Ferritin was available in 241 patients.
+ Cumulative doses available in 183 patients (out of 381 without cirrhosis, AS-AIH and treated with AZA). Doses are expressed in cumulative doses of prednisone (converted from budesonide in patients treated with this drug).
$ Cumulative doses available in 374 patients.

AZA: Azathioprine; AS-AIH: Acute-Severe Autoimmune Hepatitis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; INR: International normalized ratio; ANA: Antinuclear Antibodies; ASMA: Anti-Smooth Muscle Antobodies; IgG: Immunoglobulin G.

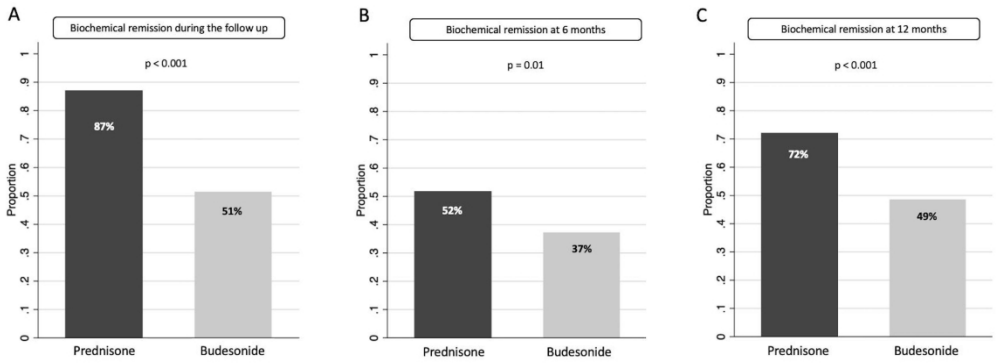
Table 2. Baseline characteristics of patients without cirrhosis and without AS-AIH treated with budesonide + azathioprine and prednisone + azathioprine according to the achievement of biochemical response.

	Budesonide			Prednisone		
	Responders (N=54)	**Non-responders (N=51)**	**P value**	**Responders (N=240)**	**Non-responders (N=36)**	**P value**
Female gender (n, %)	38 (70.4)	37 (72.6)	0.805	164 (68.4)	29 (80.6)	0.136
Age, years median, IQR)	57.6 (45.9 – 68.2)	63.1 (45.9 – 74.5)	0.122	61.8 (49.2 – 70.3)	57.4 (43.6 – 63.5)	0.061
Other AI disease (n, %)	14 (25.9)	11 (21.6)	0.600	75 (31.4)	10 (27.8)	0.663
AST, IU/L (median, IQR)	120 (59 – 433)	165 (92 – 324)	0.785	636 (160 – 1091)	706 (319 – 1268)	0.376
ALT, IU/L (median, IQR)	203 (88 – 549)	197 (110 – 475)	0.928	736 (257 – 1356)	774 (376 – 1394)	0.615
ALP, IU/L (median, IQR)	106 (80 – 183)	125 (92 – 191)	0.354	161 (113 – 250)	154 (107 – 225)	0.508
GGT, IU/L (median, IQR)	75 (34 – 161)	125 (59 – 332)	0.015	185 (92 – 306)	127 (87 – 308)	0.226
Bilirubin, mg/dL (median, IQR)	1 (0.7 – 1.6)	1 (0.6 – 1.7)	0.746	2.1 (0.9 – 7.1)	2.5 (0.8 – 9.6)	0.936
INR (median, IQR)	1 (1 – 1.2)	1 (1 – 1.1)	0.837	1.1 (1 – 1.2)	1.2 (1 – 1.2)	0.073
ANA≥1/80 (n, %)	40 (75.5)	39 (79.6)	0.619	184 (79)	25 (71.4)	0.315
ASMA≥1/40 (n, %)	29 (55,8)	21 (45.7)	0.317	125 (53.9)	19 (54.3)	0.964
IgG, mg/dL (median, IQR)	1636 (1009 – 2051)	1963 (1400 – 2410)	0.050	1790 (1420 – 2300)	2220 (1685 – 2908)	0.043
Ferritin ng/mL (median, IQR)	150 (71 – 337)	149 (48 – 475)	0.931	269 (80 – 874)	219 (107 – 652)	0.971
Biliary Changes (n, %)	4 (7.8)	6 (12.8)	0.421	32 (14.9)	5 (15.6)	0.921

AI: Autoimmune; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; INR: International normalized ratio; IgG: Immunoglobulin G; ANA: Anti-nuclear antibodies; ASMA: Anti-Smooth Muscle Antibodies

Table 3. Most frequent adverse events during follow-up.

	Entire cohort	Prednisone	Budesonide
Diabetes Mellitus n (%)	15 (13.2)	14 (15.2)	1 (4.5)
Osteoporosis n (%)	14 (12.3)	14 (15.2)	0 (0)
Acne n (%)	6 (5.3)	4 (4.4)	2 (9.1)
Edema n (%)	6 (5.3)	4 (4.4)	2 (9.1)
Arterial Hypertension n (%)	5 (4.4)	4 (4.4)	1 (4.5)
Myalgia n (%)	5 (4.4)	3 (3.3)	2 (9.1)
Psychosis n (%)	4 (3.5)	4 (4.4)	0 (0)
Weight gain n (%)	2 (1.8)	0 (0)	2 (9.1)
Others n (%)	56 (49.8)	44 (48.7)	12 (54.5)
Total	113 (100)	91 (100)	22 (100)



Biochemical response in the prednisone and budesonide cohorts in patients without cirrhosis, without AS-AIH and treated with AZA. Patients treated with prednisone presented significant higher biochemical response rates.
A: Biochemical response during follow-up. B: Biochemical response at 6 months. C: Biochemical response at 12 months

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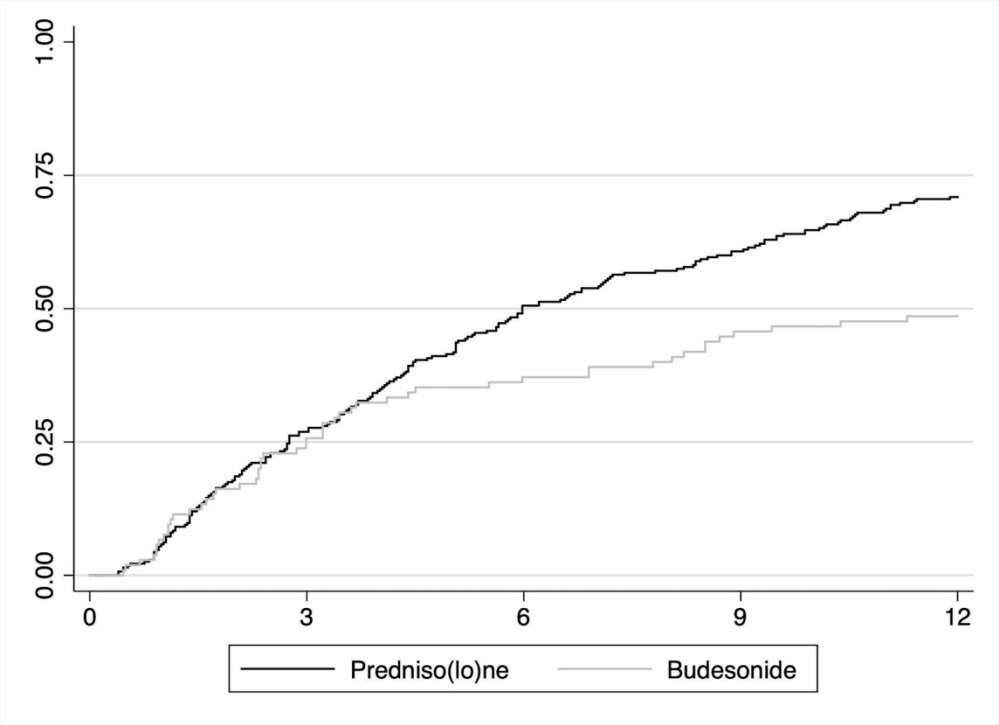

Kaplan-Meier curve with the probability of achieving biochemical remission during follow-up

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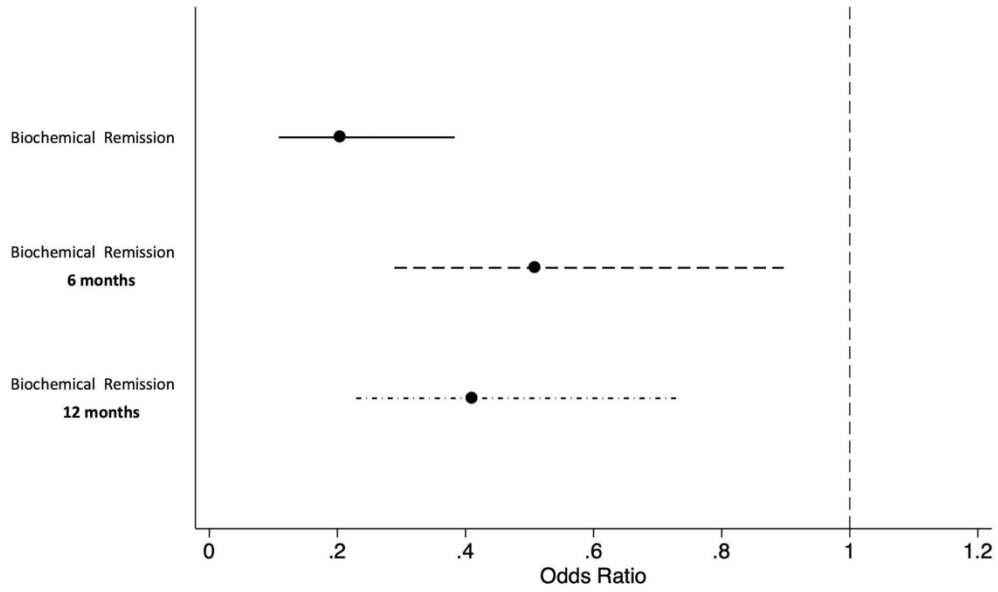

Probability of response after the application of the IPTW in patients without cirrhosis, without AS-AIH and treated with AZA. Patients treated with budesonide presented a significantly lower probability of biochemical response.

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Supplementary table 1. Median values of transaminases, IgG and drug doses.

Prednisone						
	6 months		12 months		Last follow-up	
	Responders	Non-responders	Responders	Non-responders	Responders	Non-responders
AST (median, IQR)	26.5 (23 - 31)	60 (45 – 84.5)	25 (21 – 30)	52.5 (45 – 68)	25 (20 – 32)	43.5 (30 – 61)
ALT (median, IQR)	26 (20 – 33)	63.5 (46 – 89)	23 (18 – 30)	54.5 (45 – 82)	23 (16 – 32)	47 (27 – 86)
IgG (median, IQR)	1094.5 (880 – 1300)	1454 (1220 – 1605)	1101 (960 – 1300)	1358 (1198 – 1578)	1130 (940 – 1350)	1240 (1120 – 1340)
Dose (median, IQR)	7.5 (5 – 10)	8.75 (5 – 10)	5 (2.5 – 7.5)	5 (2.5 – 7.5)	0 (0 – 0)	0 (0 – 5)

Budesonide						
	6 months		12 months		Last follow-up	
	Responders	Non-responders	Responders	Non-responders	Responders	Non-responders
AST (median, IQR)	26 (20 – 29)	44 (32 – 59)	23 (19 – 30)	42 (30 – 66)	24 (18 – 31)	32 (24 – 45)
ALT (median, IQR)	24 (17 – 30)	47.5 (30 – 74)	21 (16 – 28)	41 (24 – 69)	21 (15 – 34)	29 (20 – 59)
IgG (median, IQR)	1250 (960 – 1352)	1431 (1164 – 1352)	1230 (980 – 1373)	1455 (1219 – 1640)	1220 (901 – 1373)	1320 (1192 – 1700)
Dose (median, IQR)	3 (0 – 6)	3 (0 – 9)	0 (0 – 3)	3 (0 – 3)	0 (0 – 0)	0 (0 – 3)

AST:aspartate aminotransferase, ALT: alanine aminotransferase, IgG: immunoglobulin G, IQR: interquartile range

Supplementary table 2. Multivariate analysis.

Biochemical Remission at 6 months				
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Treatment	0.54 (0.34 – 0.87)	0.011	0.16 (0.05 – 0.47)	0.001
Age	0.99 (0.98 – 1.01)	0.865		
Gender	0.81 (0.53 – 1.27)	0.367		
AST	0.99 (0.99 – 1.00)	0.822		
ALT	0.99 (0.99 – 1.00)	0.929		
AP	0.99 (0.99 – 1.00)	0.151		
GGT	0.99 (0.99 – 1.00)	0.318		
Total Bilirubin	1.02 (0.98 – 1.05)	0.360		
INR	0.41 (0.09 – 1.84)	0.243		
ANA	1.6 (0.97 – 2.65)	0.063	2.19 (0.84 – 5.68)	0.105
ASMA	1.3 (0.88 – 2.00)	0.180		
IgG (<1.9xULN)	0.65 (0.36 – 1.19)	0.166	1.77 (0.45 – 6.88)	0.406
Ferritin (>2.1xULN)	0.77 (0.44 – 1.35)	0.360	0.25 (0.08 – 0.82)	0.023
Interface hepatitis	1.47 (0.79 – 2.75)	0.224		
Lymphoplasmacytic infiltration	3.25 (1.04 – 10.17)	0.043	1.23 (0.14 – 10.5)	0.848
Biliary changes	1.09 (0.59 – 2.02)	0.775		
Cumulative doses	0.99 (0.99 – 1.00)	0.780		
Drug suspension before 6 months	0.54 (0.25 – 1.14)	0.109	0.58 (0.17 – 1.90)	0.374
Biochemical Remission at 12 months				
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Treatment	0.36 (0.23 – 0.58)	<0.001	0.29 (0.10 – 0.82)	0.019
Age	1.00 (0.99 – 1.01)	0.537		

Gender	0.67 (0.42 – 1.09)	0.107		
AST	1.00 (0.99 – 1.00)	0.521		
ALT	1.00 (0.99 – 1.00)	0.321		
AP	0.99 (0.99 – 1.00)	0.177		
GGT	0.99 (0.99 – 1.00)	0.715		
Total Bilirubin	1.03 (0.99 – 1.08)	0.128		
INR	0.39 (0.08 – 1.86)	0.237		
ANA	0.76 (0.45 – 1.31)	0.328		
ASMA	1.09 (0.71 – 1.70)	0.691		
IgG (<1.9xULN)	0.70 (0.38 – 1.28)	0.250	0.83 (0.22 – 3.12)	0.791
Ferritin (>2.1xULN)	1.25 (0.68 – 2.29)	0.478	0.52 (0.19 – 1.47)	0.221
Interface hepatitis	1.75 (0.93 – 3.25)	0.081	1.60 (0.43 – 5.90)	0.479
Lymphoplasmacytic infiltration	2.34 (0.88 – 6.25)	0.088	1.43 (0.15 – 13.27)	0.752
Biliary changes	1.20 (0.61 – 2.34)	0.600		
Cumulative doses	1.00 (0.99 – 1.00)	0.321		
Drug Suspension before 12 months	0.57 (0.32 – 1.05)	0.075	0.78 (0.31 – 1.99)	0.618
Remission during follow-up				
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Treatment	0.16 (0.09 – 0.27)	<0.001	0.15 (0.07 – 0.33)	<0.001
Age	1.00 (0.98 – 1.02)	0.586		
Gender	0.69 (0.40 – 1.21)	0.201		
AST	1.00 (0.99 – 1.00)	0.136		
ALT	1.00 (1.00 – 1.00)	0.041	0.99 (0.99 – 1.00)	0.060
AP	0.99 (0.99 – 1.00)	0.799		
GGT	0.99 (0.99 – 1.00)	0.607		
Total Bilirubin	1.05 (1.00 – 1.12)	0.042	1.08 (0.98 – 1.19)	0.097
INR	1.33 (0.22 – 8.02)	0.756		

ANA	1.12 (0.63 – 2.01)	0.679		
ASMA	1.21 (0.74 – 1.99)	0.441		
IgG (<1.9xULN)	0.67 (0.34 – 1.29)	0.235	0.35 (0.15 – 0.86)	0.022
Ferritin (>2.1xULN)	1.26 (0.64 – 2.51)	0.493	0.92 (0.37 – 2.24)	0.856
Interface hepatitis	1.5 (0.77 – 3.03)	0.220		
Lymphoplasmacytic infiltration	1.9 (0.68 – 5.37)	0.214		
Biliary changes	0.97 (0.47 – 2.01)	0.939		
Cumulative doses	1.00 (0.99 – 1.00)	0.116		

Supplementary table 3. Standardized mean differences after the application of the inverse probability of treatment weighting (IPTW) propensity score.

Patients without cirrhosis, AS-AIH and treated with azathioprine		
	STD (%) pre-IPTW	**STD (%) post-IPTW**
Female sex	4.5	10.1
Age, years	6.2	16.1
AST, IU/L	81.3	20.9
ALT, IU/L	72.3	17.4
ALP, IU/L	28.3	0.4
GGT, IU/L	14.1	7.1
Bilirubin, mg/dL	71	13.4
INR	34.3	9.2
ANA ≥1/80	2.3	15.5
ASMA ≥1/40	9.5	6.7
IgG mg/dL	12.1	9.5
Ferritin >2.1-fold-ULN	46.8	3.3
Entire cohort		
	STD (%) pre-IPTW	**STD (%) post-IPTW**
Female sex	1.0	11.2
Age, years	9.4	3.4
Cirrhosis	39.6	16.7
AST, IU/L	82.5	6.3
ALT, IU/L	64.1	7.5
ALP, IU/L	34.3	9.1
GGT, IU/L	24.2	0.6
Bilirubin, mg/dL	76.3	0.7
INR	4.7	10.5
ANA ≥1/80	4.3	7.4
ASMA ≥1/40	16.1	1.1
IgG mg/dL	22.0	9.7
Azathioprine	8.4	1.2
Ferritin >2.1-fold-ULN	49.6	4.9

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; INR: International normalized ratio; IgG: Immunoglobulin G; ANA: Anti-nuclear antibodies; ASMA: Anti-Smooth Muscle Antibodies

Supplementary Table 4. Baseline characteristics of the entire cohort.

	Global cohort (N=597)	Budesonide (N=151)	Prednisone (N=446)	P values
Female sex (n, %)	421 (70.5)	107 (70.9)	314 (70.4)	0.915
Age, years (median, IQR)	61.9 (48.8 – 71.5)	62.2 (46.3 – 71.5)	61.8 (49.7 – 71.5)	0.591
Other AI disease (n, %)	175 (29.4)	36 (23.8)	139 (31.3)	0.082
Cirrhosis (n, %)	87 (14.7)	8 (5.4)	79 (17.8)	<0.001
AST, IU/L (median, IQR)	373 (112 – 961)	122 (71 – 330)	600 (160 – 1118)	<0.001
ALT, IU/L (median, IQR)	457 (160 – 1093)	175 (88 – 474)	618 (222 - 1267)	<0.001
ALP, IU/L (median, IQR)	153 (103 – 258)	115 (83 – 184)	166 (116 – 262)	<0.001
GGT, IU/L (median, IQR)	150 (70 – 308)	89 (45 – 263)	169 (85 – 325)	<0.001
Bilirubin, mg/dL (median, IQR)	1.6 (0.8 – 6.6)	0.9 (0.6 – 1.6)	2.4 (0.9– 8.3)	<0.001
INR (Median, IQR)	1.1 (1 – 1.3)	1 (1 – 1.2)	1.1 (1.0 – 1.3)	<0.001
Ferritin (median, IQR) *	205 (80 – 792)	146 (53 – 332)	268 (97 – 1222)	<0.001
Ferritin >2.1xULN (n, %) *	106 (30)	15 (15)	91 (36)	<0.001
ANA ≥1/80 (n, %)	443 (78.4)	114 (79.7)	329 (78)	0.659
ASMA ≥1/40 (n, %)	309 (55.7)	68 (49.6)	241 (57.7)	0.101
IgG mg/dL (median, IQR)	1800 (1400 – 2470)	1713 (1290 – 2376)	1845 (1411 – 2520)	0.061
Interface hepatitis (n, %)^	437 (84.8)	115 (85.8)	322 (84.5)	0.717

Lymphoplasmacytic infiltration (n, %)^	487 (94.4)	130 (96.3)	357 (93.7)	0.261
Biliary Changes (n, %)	67 (13.1)	16 (11.8)	51 (13.5)	0.627
Simplified AIH score (Median, IQR)	6 (6 – 8)	6 (6 – 7)	6 (6 – 8)	0.082
Cumulative doses at 6 months+ (median, IQR)	3262 (2449 – 4106)	3517 (2449 – 4597)	3234 (2514 – 3853)	0.133
Cumulative doses at 12 months+ (median, IQR)	4460 (3262 – 5966)	4545 (2973 – 7065)	4324 (3300 – 5352)	0.302
Azathioprine (n, %)	530 (88.8)	131 (86.8)	399 (89.5)	0.362

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; INR: International normalized ratio; IgG: Immunoglobulin G; ANA: Anti-nuclear antibodies; ASMA: Anti-Smooth Muscle Antibodies, IQR: Interquartile range

*Ferritin available in 353 patients.
+ Cumulative doses available in 289 patients. Doses are expressed in cumulative doses of prednisone (converted from budesonide in patients treated with this drug).
$ Cumulative doses available in 374 patients.

Supplementary Table 5. Prediction of remission according to speed of response. Full biochemical and clinical evolutionary events and data during follow-up were available in 369 patients.

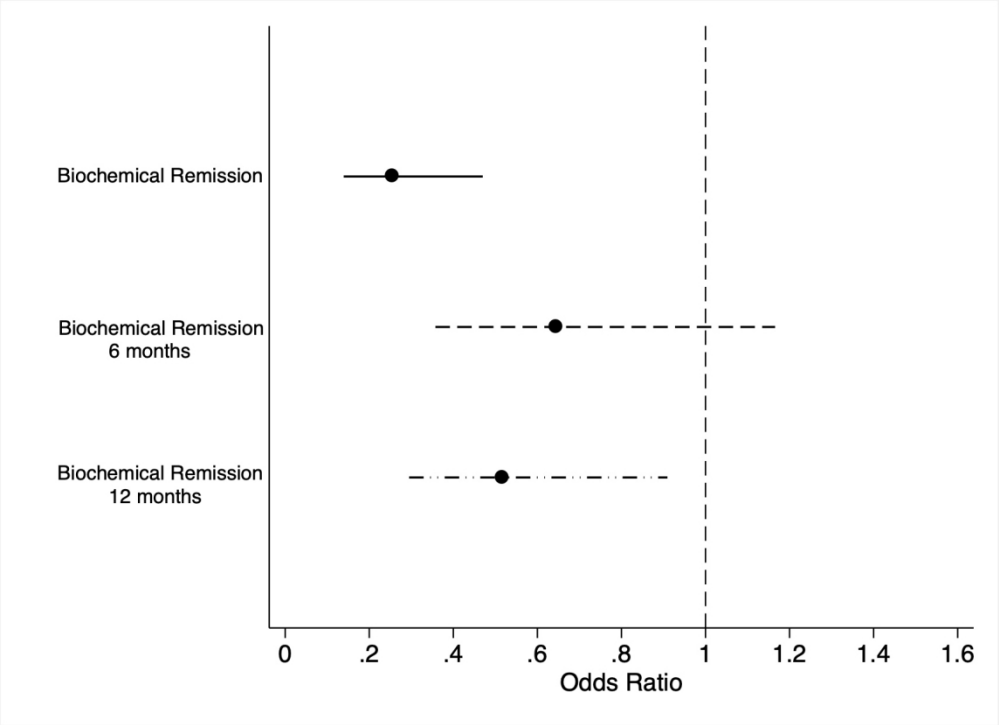
RAPID RESPONDERS BY AST DECLINE (n = 106)				
	Univariate analysis	P value	Multivariate Analysis	P value
Biochemical response at 6 months	1.55 (95% CI 0.92 – 2.62)	0.101	2.31 (95% CI 1.13 – 4.72)	0.021
Biochemical response at 12 months	1.23 (95% CI 0.71 – 2.17)	0.457	1.57 (95% CI 0.74 – 3.32)	0.234
RAPID RESPONDERS BY ALT DECLINE (n = 85)				
Biochemical response at 6 months	2.45 (95% CI 1.48 - 4.05)	<0.001	2.89 (95% CI 1.56 – 5.39)	0.001
Biochemical response at 12 months	2.08 (95% CI 1.21 – 3.57)	0.008	2.45 (95% CI 1.26 – 4.79)	0.008
RAPID RESPONDERS BY COMBINED ALT AND AST DECLINE (n = 74)				
Biochemical response at 6 months	2.39 (95% CI 1.41 – 4.06)	0.001	3.26 (95% CI 1.65 – 6.42)	0.001
Biochemical response at 12 months	2.06 (95% CI 1.16 – 3.64)	0.013	2.71 (95% CI 1.31 – 5.63)	0.007

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

Supplementary table 6. Prediction of response according to speed of response in the prednisone and budesonide cohorts. Full biochemical and clinical evolutionary events and data during follow-up was available in 369 patients.

PREDNISONE COHORT (n = 218)				
RAPID RESPONDERS BY AST DECLINE				
	Univariate analysis	P value	Multivariate Analysis	P value
Biochemical response at 6 months	1.60 (95% CI 0.82 – 3.11)	0.164	2.69 (95% CI 1.11 – 6.58)	0.029
Biochemical response at 12 months	1.13 (95% CI 0.54 – 2.39)	0.742	1.52 (95% CI 0.56 – 4.14)	0.406
RAPID RESPONDERS BY ALT DECLINE				
Biochemical response at 6 months	2.38 (95% CI 1.24 – 4.54)	0.008	3.66 (95% CI 1.62 – 8.26)	0.002
Biochemical response at 12 months	1.84 (95% CI 0.89 – 3.77)	0.095	2.86 (95%CI 1.14 – 7.12)	0.024
RAPID RESPONDERS BY COMBINED ALT AND AST DECLINE				
Biochemical response at 6 months	2.19 (95% CI 1.13 – 4.26)	0.020	3.74 (95% CI 1.59 – 8.83)	0.003
Biochemical response at 12 months	1.79 (95% CI 0.86 – 3.77)	0.121	3.09 (95% CI 1.17 – 8.16)	0.023
BUDESONIDE COHORT (n = 151)				
RAPID RESPONDERS BY AST DECLINE				
	Univariate analysis	P value	Multivariate Analysis	P value
Biochemical response at 6 months	1.11 (95% CI 0.44 – 2.79)	0.829	2.26 (95% CI 0.59 – 8.72)	0.235
Biochemical response at 12 months	0.93 (95% CI 0.37 – 2.38)	0.888	1.62 (95% CI 0.44 – 5.9)	0.463
RAPID RESPONDERS BY ALT DECLINE				
Biochemical response at 6 months	2.22 (95% CI 0.97 – 5.11)	0.059	1.85 (95% CI 0.64 – 5.32)	0.253
Biochemical response at 12 months	2.08 (95% CI 0.89 – 4.88)	0.091	1.88 (95% CI 0.65 – 5.48)	0.245
RAPID RESPONDERS BY COMBINED ALT AND AST DECLINE				
Biochemical response at 6 months	2.24 (95% CI 0.89 – 5.59)	0.084	2.61 (95% CI 0.78 – 8.79)	0.121
Biochemical response at 12 months	1.95 (95% CI 0.77 – 4.97)	0.161	2.06 (95%CI 0.61 – 6.97)	0.243

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.



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