



REVIEW

Budesonide in the first line treatment of patients with autoimmune hepatitis



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Abstract Budesonide is a glucocorticoid characterized by its local action, with a low systemic bioavailability. Since the original trial comparing budesonide with prednisone in 2010, it is recommended as an effective alternative for the treatment of non-severe acute or chronic autoimmune hepatitis. In this document, we review the general pharmacologic properties of glucocorticoids, the available evidence for the use of budesonide as first line option for autoimmune hepatitis as well as the safety profile of the drug.

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PALABRAS CLAVE

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Budesonida en primera línea de tratamiento de pacientes con hepatitis autoinmune

Resumen La budesonida es un glucocorticoide que se caracteriza por su acción local, con una baja biodisponibilidad sistémica. Desde el ensayo original publicado en 2010, en el que se comparó la budesonida con prednisona, se recomienda como una alternativa eficaz en el tratamiento de los pacientes con hepatitis autoinmune aguda o crónica no grave. En este documento, revisamos las propiedades farmacológicas generales de los glucocorticoides, la evidencia disponible para el uso de budesonida como fármaco de primera línea en estos pacientes, así como el perfil de seguridad del fármaco.

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Background

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease endowed with a progressive course. This condition is characterized by hypertransaminasemia, elevation of gammaglobulines and the presence of autoantibodies. Histologically, the typical findings are interface hepatitis and lymphoplasmacytic portal infiltrate.¹ The exact pathogenesis of AIH is unknown. Nevertheless, different hypotheses point towards environmental agents that may trigger T cells-mediated immune response to liver antigens in a genetically predisposed host.² Interestingly, although AIH was the first liver disease with a targeted treatment in the early 60s, it is still a challenging scenario where treatment options have not evolved significantly. In fact, this therapeutic armamentarium mainly consists of inducing remission with prednisone associated with a long-term use of steroid-sparing drugs, usually azathioprine.^{1,3} However, international guidelines also recommend budesonide as an alternative first line agent in patients without cirrhosis or severe AIH^{1,3} (defined as INR >1.5 and <2 and/or total bilirubin $\geq$ 12 mg/dL⁴).

The aim of this review is to deepen into the current knowledge and available evidence of budesonide as first-line option in the treatment of AIH.

General pharmacologic characteristics of glucocorticoids

Glucocorticoids are natural steroid hormones secreted by the adrenal gland, whose production is regulated by the hypothalamic–anterior pituitary–adrenocortical axis, being cortisol the most relevant glucocorticoid. Briefly, corticotrophin-releasing hormone induces the release of adrenocorticotrophic hormone (ACTH) in the anterior pituitary, stimulating the delivery of cortisol from the adrenal gland.⁵ Moreover, cortisol production is characterized by a circadian pattern, with the highest plasma concentrations in the morning and the lowest at night.⁵ This hormone exhibits a plethora of effects involving almost every organ, probably being the anti-inflammatory effects the most recognized ones. Thus, synthetic analogues of cortisol have been developed by means of structural modifications in the glucocorticoid nucleus, enhancing the anti-inflammatory effect and decreasing the mineralocorticoid activity and being used for treating a wide range of inflammatory and immune-mediated diseases.⁵ These modifications confer an increased specificity for the glucocorticoid receptor, with a longer efficacy and an increased lipophilicity. The bioavailability of the drug after oral ingestion ranges from 60 to 100%, with a moderate protein binding to transcortin and albumin, being the free fraction the responsible of both desired and undesired effects.⁶

Prednisone

Prednisone is a prodrug transformed by 11 β -hydroxysteroid dehydrogenase-1 into prednisolone, the active drug. After ingestion, plasma concentrations reach its peak in 0.5–3 h, with a reported bioavailability of 84 $\pm$ 13%.⁶ Cortisol and prednisolone share a comparable biochemical structure,

although the latter presents a double bond C1=C2, contributing to its higher affinity to the glucocorticoid receptor and leading to a 4 times higher activity than cortisol.⁷

As mentioned before, AIH was the first liver disease with a specific treatment, being prednisone the drug of choice. The evidence comes from the original clinical trials run in the 70s and 80s, where untreated patients had a dismal evolution, while those under corticosteroid therapy improved their liver tests and had longer survivals. A summary of these trials is captured in [Table 1](#).

Budesonide

Under a structural point of view, budesonide is a 17- α substituted steroid obtained by modifying the 6- α -hydroxy-prednisolone nucleus by adding a 16 α and 17 α acetyl group.⁸ The introduction of lipophilic constituents at the 17- α and 16- α positions increases tissue penetration and drug potency.⁸ In fact, it is a potent topical anti-inflammatory agent⁹ with an affinity for the glucocorticoid receptor 195 times greater than hydrocortisone and 15 times higher than prednisolone.^{10,11} Mechanistically, budesonide activates glucocorticoid receptors in the cytoplasm allowing its translocation to the nucleus, preventing the transcription of inflammatory genes by binding to cortisol binding protein and decreasing cytokine production by activating HDCA2.¹² When administered orally, the systemic bioavailability of budesonide is around 10%, as the 90% of the drug is cleared in the hepatic first-pass clearance.^{13,14} The metabolism of budesonide is predominantly driven by CYP3A4, obtaining the two most relevant metabolites: 6 β -OH-budesonide and 16 α -OH-prednisolone, both presenting a marginal glucocorticoid activity.¹⁵ Although budesonide is not characterized by presenting many drug-to-drug interactions, some drugs should be used cautiously when administered concomitantly. Hence, cytochrome P450 inhibitors such as ketoconazole, azithromycin or protease inhibitors, among others, may increase plasma exposure of budesonide, and the combination should be avoided.¹⁶ On the other hand, CYP3A4 inducers (phenobarbital, carbamazepine, phenytoin) reduce budesonide exposure, decreasing its effectiveness.¹⁶

Budesonide as first line drug for autoimmune hepatitis

The usefulness of budesonide in the treatment of AIH was formerly evaluated in the seminal study carried out by Danielsson,¹⁷ in the early 1990s. However, it was not until 2005 where the first trial evaluating this drug in untreated patients was published.¹⁸ In this open one-arm multicenter phase IIa trial, the authors evaluated the ability of budesonide in inducing response in these patients, by measuring the drop of transaminases three months after starting the treatment. The authors showed that budesonide was not only effective in reducing transaminase levels below twice the upper limit of normal, but also reducing IgG and gammaglobulines.¹⁸ Furtherly, Manns et al. published the only currently available trial comparing prednisone and budesonide as first line therapies in the management of AIH.¹⁴ Budesonide was not only effective, but also superior to prednisone. In fact, 47% of patients treated with

Table 1 Clinical trials evaluating prednisone for treating autoimmune hepatitis.

Study	Country	Design	Criteria	Patients	Treatment	Follow-up	End-point	Results	Side-effects
Cook et al., 1971 ³⁴	USA	Unblinded, randomized, controlled trial	Untreated patients diagnosed of active chronic hepatitis	N = 54	Corticosteroid group (n = 22): PDN 15 mg/day reduced whenever biochemical liver function test became normal or in the emergence of severe side-effects Control group (n = 27)	72 months	Mortality at 72 months TB, AST, albumin at 72 months	Mortality: PDN 3/22 (13.6%) untreated group 15/27 (55.5%) (p < 0.01) Albumin was significantly higher in the PDN group compared to the control group at 6, 12, 18 and 24 months. TB was significantly lower in PDN group with respect to the control group at six and 24 months.	PDN: obesity 5/22 (23%), moon face 5/22 (23%), acne 4/22 (18%), Osteoporosis and vertebral collapse 2/22 (9%), Perforated duodenal ulcer 1/22 (5%), acute steroid psychosis 1/22 (5%), terminal bronchopneumonia 1/22 (5%), myositis 1/22 (5%)
Soloway et al., 1972 ³⁵	UK	Randomized, double-blinded, controlled trial	Hepatic disease documented by clinical, biochemical, and histological abnormalities lasting at least 10 weeks and documented by biopsy, jaundice, or AST $\geq 10 \times$ ULN or $\geq 5 \times$ ULN plus IgG $\geq 2 \times$ ULN	N = 63	(a) PDN (n = 18) 60 mg daily for one week, 40 mg daily the following week, 30 mg daily for two weeks and 20 mg daily as maintenance therapy. (b) AZA (n = 14) 100 mg daily. (c) PDN + AZA (n = 14): 30 mg daily for 1 week, 20 mg daily the following week, 15 mg daily for 2 weeks, and 10 mg daily as maintenance (d) Placebo (n = 17)	3–38 months	(1) Remission defined as: (a) clinical normality, return to all customary activities PLUS (b) Disappearance of histological signs of disease activity normality or of minor changes indistinguishable from those in nonspecific or chronic persistent hepatitis (2) Mortality	PDN group: remission 8/18 (44%), mortality 1/18 (6%), PDN + AZA group: remission 3/14 (21%), mortality 1/14 (7%). AZA group: remission 1/14 (7%), mortality 5/14 (36%) Placebo group: remission 0/17 (0%), mortality 7/17 (41%) Response rate in patients receiving PDN or combined treatment were superior to those receiving AZA or placebo	PDN: cushingoid appearance 13/18 (72%), serious side effects (vertebral collapse, aseptic necrosis of the femoral head, or cataracts) 3/18 (17%), diabetes requiring insulin 1/18 (6%)

Table 1 (Continued)

Study	Country	Design	Criteria	Patients	Treatment	Follow-up	End-point	Results	Side-effects
Murray-Lyon et al., 1973 ³⁶	USA	Randomized, double-blind, controlled trial	Active chronic hepatitis defined by hepatic disease lasting at least for 3 months with AST $\geq$ 100 IU/L and/or IgG > 1.5 g/100 mL. Patients previously treated with AZA or corticosteroids were not excluded.	N = 47 Cirrhosis (n = 32)	PDN group (n = 22): 5 mg every 8 h AZA group (n = 25): 75 mg daily In the absence of response or AST persistently $\geq$ 200 IU/L, PDN or AZA doses were increased to 20 mg or 112.5 mg respectively.	24 months	Survival at 24 months	PDN group: 95% probability of survival at 24 months AZA group: 72% probability of survival at 24 months Significant ($p < 0.005$) decrease in bilirubin and globulin in both groups Higher AST ($p < 0.05$) and IgG ($p = 0.02$) decrease in the first 6 months in patients treated with PDN.	PRD: facial mooning 11/22 (50%), diabetes mellitus 3/22 (14%); hypertension 2/22 (9%), brush fracture of thoracic vertebrae 1/22 (5%)
Summerskill et al., 1975 ³⁷	USA	Multicenter, randomized, double-blind, controlled trial	Hepatic disease documented by clinical, biochemical, and histological abnormalities lasting at least 10 weeks and documented by biopsy, jaundice, or AST $> 10 \times$ ULN or $> 5 \times$ ULN plus IgG $> 2 \times$ ULN	N = 120	(a) Placebo (n = 16) (b) AZA 100 mg (n = 13) (c) PDN (n = 30) (d) PDN + AZA (n = 30) (e) PDN at titrated doses attending to biochemical evolution (n = 31)	36 months	(1) Remission defined as: (a) Absence of symptoms and return of the patient to customary activities PLUS (b) AST $\leq 2 \times$ ULN PLUS (c) Normalization of immunoserological tests (2) Mortality	PDN: 24/30 (80%) achieved remission. Mortality 3/30 (10%) PDN + AZA: 24/30 (80%) achieved remission. Mortality 2/31 (7%) Titrated PDN: 23/31 (74%) achieved remission. Mortality 2/31 (7%) Placebo or AZA: 10/29 (34%) achieved remission. Mortality 12/29 (41%).	PDN: severe cosmetic changes 4/30 (13%), diabetes 4/30 (13%), cataracts 2/30 (7%) vertebral collapse 1/30 (3%) PDN/AZA: diabetes 3/30 (10%) Titrated PDN: diabetes 3/31 (10%) Pacebo or AZA: gastrointestinal bleeding 5/29 (17%)
Tage-Jansen et al., 1982 ³⁸	Denmark	Multicenter, randomized, unblinded clinical trial	Patient with biopsy-proven chronic aggressive hepatitis.	N = 99* only information for 84 patients	(a) PDN 10 mg/day if weight < 70 kg or 15 mg/kg if weight $\geq$ 70 kg. (b) AZA 10 mg/kg.	38 (12–83 months)	(1) Remission defined as (a) AST < 40 UI/L (b) IgG < 15.1 g/L (2) Mortality	PRD: Remission: 21/47 (45%); mortality: 13/27 (28%) AZA: Remission: 6/37 (37%), mortality: 10/37 (27%)	Not reported

TB: total bilirubin; AST: aspartate aminotransferase; PDN: prednisone; AZA: azathioprine; IgG: immunoglobulin G; ULN: upper limit of normal; CALD: chronic active liver disease.

Adapted from Lammers et al.³⁹

budesonide reached the primary endpoint, while only 18.4% of those treated with prednisone did it. These unexpected results may be explained by the unconventional definition of the primary endpoint, as it was a composite one gathering biochemical remission with the absence of adverse events related to corticosteroids. It is worth mentioning that this unusual endpoint was also used in a similar trial done in AIH pediatric patients.¹⁹ However, the results were remarkably different, as the primary endpoint was only reached in 16% and 15% of patients treated with budesonide and prednisone, respectively.¹⁹

Beyond these trials, the evidence is limited. Delgado et al. published the results of a large retrospective multicenter cohort of AIH patients in Israel.²⁰ Biochemical remission was achieved in 63% of patients treated with budesonide plus azathioprine and 54.9% of patients treated with the combination of prednisone plus azathioprine. However, 15% of these patients included were also diagnosed with overlap syndrome and, notably, budesonide (or the combination of budesonide and azathioprine) was used only in 21 patients. In this regard, a recent work from Turkey retrospectively evaluated this scenario.²¹ In their work, they included 50 untreated AIH patients: 25 treated with budesonide plus azathioprine and 25 with the combination of prednisone and azathioprine. Although they did not identify differences in biochemical remission, inflammatory activity, indirectly measured by median transaminase levels, was lower than in any other study -or in the real-life setting- and, more importantly, the definition they used did not consider the normalization of IgG (or gammaglobulin), potentially limiting the evaluation of the results. These studies and others evaluating budesonide as first line alternative are summarized in Table 2.

Despite the good results obtained in phase II and phase III trials, the use of budesonide in naïve AIH patients is rare.^{22,23} Of note, an international multicenter survey disclosing the current management of the disease in different worldwide centers with recognized expertise in the treatment of AIH patients, evidenced that budesonide was not used in any center as first line option for the induction of disease remission. The reason for this paucity of use is probably the consequence of the generalized perception of lower efficacy. A recent multicenter Spanish work, presented in the 2021s Spanish Association for the Study of the Liver annual meeting, showed that budesonide use was marginal (only 5.4% of the cohort) and, more importantly, it was significantly inferior to prednisone.²⁴ In terms of efficacy, the authors compared the two cohorts through an Inverse Probability Treatment Weighting (IPTW) propensity score, identifying that those patients treated with budesonide presented a lower probability of reaching biochemical response at 6 months (OR 0.44; CI95% 0.24–0.81; $p < 0.009$), at 12 months (OR 0.43; CI95% 0.23–0.8; $p < 0.008$) and during the follow-up (OR 0.29; CI95% 0.14–0.58; $p < 0.0001$) (Table 4).

Indications and regimen of budesonide as first line drug

In untreated patients diagnosed of non-severe acute or chronic AIH, budesonide is an adequate alternative treatment endorsed by international guidelines.^{1,3} The

recommended dose is budesonide 3 mg three times per day, combined with weight-adjusted azathioprine.³ Once biochemical response is documented, budesonide tapering during the upcoming 6 months is recommended, until reaching a dose of 3 mg daily. Once biochemical remission is consolidated, budesonide withdrawal can be considered while maintaining AZA treatment. However, due to the short life of budesonide, it is unclear whether this reduction scheme is reasonable.¹

While budesonide is an alternative in the non-severe scenario, it cannot be considered in the presence of acute liver failure or cirrhosis. First, because there is no evidence of its efficacy, as these patients were not included in the former trial. Second, because the presence of portosystemic shunts in patients with cirrhosis may decrease budesonide efficacy and increase the risk of adverse events by bypassing the liver.²⁵ Finally, some reports have warned about the increased risk of portal thrombosis in cirrhotic patients treated with budesonide, discouraging its use.³

Budesonide safety profile

Because of the marginal use of budesonide in untreated patients, the extent of information about the safety profile in this specific scenario is scant. In the original trial, patients treated with budesonide presented a significant lower rate of adverse events (AEs) compared to patients on prednisone.¹⁴ Specifically, 26% of patients in the budesonide group presented at least one AE during the follow up, being moon face, acne and hirsutism the leading causes. On the other hand, up to 51.5% of patients treated with prednisone developed at least one AE, reporting the same leading causes.¹⁴ Interestingly, no patient treated with prednisone presented diabetes as side effect, while 4 patients (15.4%) on budesonide presented this complication.

A few years later, a similar trial was carried out in the pediatric population. The authors did not identify differences in the emergence of AEs in budesonide and prednisone cohorts either at 6 or 12 months after treatment initiation.¹⁹ The data about AEs emergence in the different published studies is summarized in Table 2.

A recent Dutch study specifically evaluated the risk of developing steroid related AEs in AIH patients – including overlap with Primary Biliary Cholangitis (PBC) or Primary Sclerosing Cholangitis (PSC) – treated with low doses of prednisone or budesonide. There, they reported that prednisone exposure increased the risk of AEs (OR 1.08, CI95% 1.06–1.11), while budesonide, although bordering the statistical significance, did not (OR 1.09, CI95% 1.00–1.2).²² Nevertheless, the authors found that not only prednisone, but also budesonide significantly increased the risk of cataracts and bone fracture. In fact, these latter AEs persisted after correcting for prior prednisone use, suggesting that the use of budesonide does not avert the risk of them.

A fearsome side effect of steroids is adrenal insufficiency, as its consequences can be devastating. On this subject, a recent placebo-controlled trial of PBC patients treated with budesonide showed a slight reduction of serum cortisol in patients treated with the drug with respect to those on placebo.²⁶ However, besides some case reports describing anecdotal cases of this complication in the AIH setting,²⁷ the

Table 2 Clinical trials & retrospective studies evaluating budesonide for the treatment of autoimmune hepatitis.

Study	Country	Design	Inclusion criteria	Patients	Treatment	Followup	Primary endpoint	Results	Adverse EVENTS
Wiegand et al., 2005 ¹⁷	Germany, Netherlands	Multicenter Open label, prospective clinical trial	Untreated AIH patients AST and ALT at least >3× ULN	N = 14; finally included N = 12	Day 1: 3 g twice daily from day 2: 3 mg thrice daily. Upon biochemical remission, the dosage was individually reduced to 3 mg budesonide No other immunosuppressive drugs allowed	12 weeks	Remission defined as drop of AST and ALT ≤2×ULN.	Complete remission: 7/12 Partial response 3/12	Leukocytosis 5/14 (36%) Hypercholesterinaemia 4/14 (29%) Cushing-like symptoms 3/14 (21%)
Csepregi et al., 2006 ⁴⁰	Germany	Multicenter Open label study.	Naïve or previously treated patients diagnosed of AIH or overlap	N = 18 First-line BUD in AIH: N = 7	BUD 3 mg thrice daily	24 weeks	Not defined	Biochemical remission in AIH 4/7 No response in AIH: 3/7	Total incidence: 6/18 (33%) Weight gain >3 kg 3/18 (17%), Acne 2/18 (11%) Abdominal pain 1/18 (6%) Alopecia 1/18 (6%) Every AE emerged in patients with cirrhosis BUD: 26/100 (26%) Headache 11.8% Mood alterations 9.8%. Weight gain 5.9% Muscular weakness 4.9%. Hypertension 2.9% Insomnia 1%. PDN: 53/103 (51.5%) Weight gain 19%. Headache 7.6%. Mood alterations 7.6%. Muscular weakness 7.6%. Hypertension 6.7%. Insomnia 4.8%
Manns et al., 2010 ¹³	Germany, Poland, Ukraine, Hungary, Israel, Sweden	Prospective, 6-month double-blind, double-dummy, controlled trial	Untreated AIH patients AST and ALT at least >2× ULN	N = 207 patients BUD = 102 pat PDN = 105 pat	BUD: 9 mg/daily. PDN group: 40 mg/daily	Segment A 24 weeks Segment B 24 weeks	Biochemical remission without corticosteroid-related adverse events.	Primary endpoint: BUD: 47/100 (47.0%) PDN: 19/103 (18.4%)	

Table 2 (Continued)

Study	Country	Design	Inclusion criteria	Patients	Treatment	Followup	Primary endpoint	Results	Adverse EVENTS
Efe et al., 2012 ²⁴	Turkey, France, Italy	Multicenter, retrospective study	Untreated definite or probable AIH defined by simplified AIH criteria (IAIHG) AIH/PBC overlap syndrome according to Chazouilleres criteria. ⁵ ALT or AST levels >3×ULN	N = 18	BUD 9 mg/day + AZA 50 mg all patients	6 months	(a) Biochemical remission defined by AST and/or ALT ≤2×ULN (b) AST/ALT drop >50% after 1 month on treatment	Biochemical remission: 11/18 (61.1%) No response: 7/18 (38.9%)	Incidence 11/18 (61%) Weight gain: 6/18 (30%); acne 4/18 (20%); hirsutism: 4/18 (20%); moon face: 2/18 (10%); skin striae: 2/18 (10%); buffalo hump: 2/18 (10%)
Woynarowski et al., 2013 ¹⁸	Poland	Multicenter prospective, double-blind, randomized, controlled trial in pediatric AIH patients	Pediatric AIH patients (9–17 years) AST and ALT at least >2×ULN	N = 46 BUD = 19 pat PDN = 27 pat	3 mg 3 times daily or 3 mg twice daily after biochemical	Segmentt A 24 weeks Segment B 24 weeks	Biochemical remission without corticosteroid-related adverse events.	Primary endpoint: BUD: 3/19 (16%) PDN: 4/27 (15%)	PDN incidence 17/27 (63%); moon face: 12/27 (44%); acne: 7/27 (26%); skin striae: 3/27 (11%) BUD incidence 9/19 (47%), acne 4/19 (21%), moon face 2/19 (11%), skin striae 1/19 (5%)
Binicier et al., 2019 ²⁰	Turkey	Retrospective unicenter study	Untreated AIH patients	N = 50 PDN + AZA = 25 pat PDN + BUD = 25 pat	PRED/AZA: 30 mg/day PRED and AZA. BUD/AZA: 9 mg/day BUD and AZA.	6 months	Biochemical remission defined by AST and ALT normalization	Biochemical remission defined as transaminases normalization: - PDN + AZA: 17/25 (68%) - BUD + AZA: 18/25 (72%)	PDN/AZA incidence: 9/25 (60%), acne 4/25 (16%), moon face 4/24 (16%), hirsutism 3/25 (12%), striae 2/25 (8%), myopathy 1/25 (4%), buffalo hump 1/25 (4%). BUD/AZA Incidence 5/25 (20%) Acne 2/25 (8%), hirsutism 1/25 (4%), myopathy 1/25 (4%), moon face 1/25 (4%), buffalo hump 1/25 (4%), striae 2/25 (4%).

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; AIH: autoimmune hepatitis; BUD: budesonide; AZA: azathioprine; PDN: prednisone; pat: patients.

Table 3 International guidelines recommendations for the treatment of autoimmune hepatitis.

Guideline	Drug	Induction dose	Tapering	Azathioprine (yes/no)	Duration of treatment
AASLD 2020 ³	Prednisone	20–40 mg daily	Tapper to 5–10 mg daily	Yes	At least 2 years
	Budesonide	3 mg thrice daily	Tapper to 3 mg daily	Yes	
ESPGHAN 2019 ⁴¹	Prednisone	2 mg/kg daily (maximum 60 mg/day)	Tapper to 2.5–5 mg daily	Yes	At least 2–3 years
Hellenic 2018 ⁴²	Budesonide	Undefined	Undefined	Undefined	Undefined
	Prednisone	Prednisolone 0.5–1 mg/kg daily	Individualized according to response and side-effects Complete PDN withdrawal after 6–8 months	Yes	At least 3 years
EASL 2015 ¹	Budesonide	9 mg daily	Not defined	Yes	At least three years and 24 months after biochemical remission
	Prednisone	0.5–1 mg/kg daily	(a) From 60 to 20 mg - 10 mg weekly (b) From 20 mg to 10 mg - 2.5–5 mg biweekly (c) From 10 mg - Individualized according to response	Yes	
BSG 2011 ⁴³	Budesonide	9 mg daily	Not clearly defined	Yes	At least 2 years and 12 months after biochemical remission
	Prednisone	30 mg daily	5 mg weekly until 10 mg daily	Yes	
	Budesonide	9 mg daily	Not defined	Yes	

Table 4 Baseline characteristics of the patients included in the study by Díaz-González et al.²⁴

Centres	21 Spanish centers	
Study period	2009–2020	
	Budesonide	Prednisone
Number of patients	151	218
Women (n, %)	107 (70.9)	154 (70.6)
Age (years, median, IQR)	62,2 (46.3–71.5)	62,4 (50.7–72.1)
Cirrhosis (n, %)	8 (5.4)	38 (17.5)
Induction dose (median, IQR)	9 (9–9)	50 (30–60)
Azathioprine (n, %)	132 (88.6)	184 (86)

IQR: interquartile range.

information is very limited and comes from studies ran in the inflammatory bowel disease (IBD) scenario. There, different studies agree with the results from the PBC study²⁶: budesonide induces a mild reduction in plasma cortisol, but it is not a clinical concern at the usual doses recommended in the treatment of AIH.^{11,28} Moreover, other studies analyzing long-term use of budesonide at 3–6 mg doses have shown an absence -or very limited- of effect on adrenal function.^{29–31}

Are calcium and vitamin D supplements necessary?

As per guidelines, DEXA (dual-energy X-ray absorptiometry) scan of both vertebrae and hips should be done in patients at risk of osteoporosis at AIH diagnosis, and every 2–3 years in patients with ongoing risk factors.³ In fact, the most prevalent risk factor in AIH patients is the immunosuppressive

treatment itself, specifically the prolonged use of corticosteroids. However, the body of evidence mostly comes from the IBD setting³² where a randomized trial comparing prednisone and budesonide in patients with active Crohn's disease showed a significantly higher bone loss in patients treated with prednisone.³³ However, this was not confirmed on other studies.³⁴

Prospective long term studies evaluating impact of budesonide in the bone density of patients with AIH are lacking. However, Van den Brand et al.²² recently showed that budesonide exposure significantly increases the risk of bone fracture, reporting an OR 1.14 (CI95% 1.03–1.27). Therefore, considering the ease of use and its favorable profile, as well as the need of prolonged therapy, treatment with vitamin D and calcium is safe and probably a cost-effective approach.

Discussion

Budesonide is a potent synthetic corticosteroid with a lower systemic bioavailability because of the high first-hepatic pass clearance. Although this drug is recommended as an effective alternative by the different international societies (Table 3), its use in the real-life setting is low. Recently, a retrospective multicenter study developed in Spain showed that the probability of achieving biochemical remission in patients treated with budesonide is significantly lower than those treated by prednisone.²⁴ However, these results must be prospectively validated. In terms of safety, the former trial¹⁴ showed a lower short-term rate of AEs in patients treated with budesonide. However, recent data show that budesonide also significantly increases the risk of bone fracture and cataract.²²

In conclusion, budesonide is a safe and effective drug in the setting of AIH, but further studies are needed in order to improve patient selection for its use as first line induction therapy.

Conflict of interest

The authors declare that they have no conflict of interest.

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