Expert clinical management of autoimmune hepatitis in the real world

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Citation

Expert clinical management of autoimmune hepatitis in the real world

R. Liberal*, Y. S. de Boer[†] [iD], R. J. Andrade[‡], G. Bouma[†], G. N. Dalekos[§], A. Floreani[¶], D. Gleeson[**], G. M. Hirschfield[††], P. Invernizzi[‡‡], M. Lenzi[§§], A. W. Lohse[¶¶], G. Macedo[***], P. Milkiewicz[†††], B. Terziroli[‡‡‡], B. van Hoek[§§§], J. M. Vierling[¶¶¶] & M. A. Heneghan* on behalf of the International Autoimmune Hepatitis Group (IAIHG)[a]

*London, UK.
[†]Amsterdam, The Netherlands.
[‡]Málaga, Spain.
[§]Larissa, Greece.
[¶]Padova, Italy.
[**]Sheffield, UK.
[††]Birmingham, UK.
[‡‡]Milan, Italy.
[§§]Bologna, Italy.
[¶¶]Hamburg, Germany.
[***]Porto, Portugal.
[†††]Warsaw, Poland.
[‡‡‡]Lugano, Switzerland.
[§§§]Leiden, The Netherlands.
[¶¶¶]Houston, TX, USA.

Correspondence to:
Prof. M.A. Heneghan, Institute of Liver Studies, King's College Hospital, Denmark Hill, London SE5 9RS, UK.
E-mail: michael.heneghan@nhs.net

Rodrigo Liberal and Ynto Sjoerd de Boer contributed equally.

Authors and their complete affiliations are listed in Appendix 1.

[a]See Appendix 2 for the list of contributors.

SUMMARY

Background
High-quality data on the management of autoimmune hepatitis (AIH) are scarce. Despite published guidelines, management of AIH is still expert based rather than evidence based.

Aim
To survey expert hepatologists, asking each to describe their practices in the management of patients with AIH.

Methods
A survey questionnaire was distributed to members of the International AIH Group. The questionnaire consisted of four clinical scenarios on different presentations of AIH.

Results
Sixty surveys were sent, out of which 37 were returned. None reported budesonide as a first line induction agent for the acute presentation of AIH. Five (14%) participants reported using thiopurine S-methyltransferase measurements before commencement of thiopurine maintenance therapy. Thirteen (35%) routinely perform liver biopsy at 2 years of biochemical remission. If histological inflammatory activity is absent, four (11%) participants reduced azathioprine, whereas 10 (27%) attempted withdrawal altogether. Regarding the management of difficult-to-treat patients, mycophenolate mofetil is the most widely used second-line agent ($n = \sim450$ in 28 centres), whereas tacrolimus ($n = \sim115$ in 21 centres) and ciclosporin ($n = \sim112$ in 18 centres) are less often reported. One centre reported considerable experience with infliximab, while rescue therapy with rituximab has been tried in seven centres.

Conclusions
There is a wide variation in the management of patients with autoimmune hepatitis even among the most expert in the field. Although good quality evidence is lacking, there is considerable experience with second-line therapies. Future prospective studies should address these issues, so that we move from an expert- to an evidence- and personalised-based care in autoimmune hepatitis.

INTRODUCTION

Autoimmune hepatitis (AIH) is a severe life threatening chronic progressive immune-mediated inflammatory disorder of the liver.[1] AIH is a relatively rare disease, although its incidence has risen in recent years.[2] It affects both children and adults, and is characterised by hypergammaglobulinaemia, circulating autoantibodies and interface hepatitis.[3] Women are more often affected than men (ratio: 4:1).[3] AIH is a very heterogeneous disease with a variety of clinical presentations, ranging from asymptomatic liver biochemical abnormalities to acute severe hepatitis or even acute liver failure.[4] There is no single diagnostic test for AIH; and diagnosis is based upon several indicative clinical, biochemical, serological and histological findings.[5] Currently, two diagnostic scoring systems, the revised original (1999) and the simplified (2008) criteria, have been published by the International Autoimmune Hepatitis Group.[6, 7] In all but the mildest form of AIH, irrespective of type of presentation, fibrosis is frequently present at diagnosis, and with advanced disease bridging fibrosis and cirrhosis are often seen.[1] Untreated, this condition has a poor outcome, with mortality rate of up to 40% reported.[1] High-quality data on the management of AIH are scarce, with therapeutic data largely informed by randomised trials published over four decades ago.[8–10] In addition, decisions regarding the use of second-line therapies are based on small series or even case reports, mostly reporting the experience of a limited number of centres with a special interest in AIH.[11]

Societies such as the American Association for the Study of the Liver (2010), the British Society of Gastroenterology (2011), and more recently the European Association for the Study of the Liver (2015) published guidelines,[12–14] which include recommendations pertaining to second-line therapies in AIH, based on the limited available data. Thus, expert opinion rather than evidence-based medicine remains a factor in the management of patients with AIH.[15] The present study was designed to explore the current practices on the management of AIH of a panel comprising international expert hepatologists with extensive experience in AIH in order to help design and inform future prospective studies.

METHODS

Study design

We developed a survey questionnaire to assess the practices of an international panel of expert hepatologists on the clinical management of AIH. The participants were selected if the following criteria were met: current membership of the International Autoimmune Hepatitis Group, active practice of adult patients with AIH and expertise in AIH based on a relevant track record of publications in AIH within the last 3 years. The survey was initially distributed and tested among 15 members of the International Autoimmune Hepatitis Group who fulfilled the aforementioned criteria at their biannual meeting in Vienna in April 2015. In addition, the questionnaire was made available online, and an e-mail link to the survey was sent to further 45 experts in August 2015, followed by a total of three weekly reminders. Participants were asked to provide details on their clinical practice: number of years in practice, centre, country, approximate number of AIH patients, whether or not working at a transplant centre.

Questionnaire

The questionnaire consisted of four clinical scenarios on different presentations of AIH on which 37 questions were asked (Data S1, https://www.surveymonkey.com/r/Clin_manag_AIH). Briefly, cases consisted of a short history and results from diagnostic work-up, in short representing a 'standard' presentation of a 32-year-old woman (Case 1), follow-up on the management of a 44-year-old woman with nonresponse to standard therapy after 1 year (Case 2), a 44-year-old man with intolerance to standard therapy requiring second-line therapy (Case 3) and a 25-year-old woman with acute liver failure due to AIH (Case 4). Answers to the provided questions were offered as integer multiple choice, allowing for a free text alternative (other).

Data presentation and analysis

Data were collected non-anonymously and analysed using the graphical and analytical features of www.surveymonkey.com and Microsoft Excel 2010 (Microsoft Corporation, Washington, USA). Answers are described as counts and percentages for categorical variables. In addition, we compared the group of respondents working at a transplant centre with the group of respondents working at a nontransplant centre regarding the experience with second-line agents as well as the management of acute severe to acute liver failure due to AIH.

Ethical considerations

This study was conducted according to the Declaration of Helsinki. All authors reviewed and approved the final manuscript.

RESULTS

Participants

A total of 60 surveys were sent to the International Autoimmune Hepatitis Group members fulfilling the criteria mentioned above, out of which 37 (62%) were returned. All 37 respondents answered every question. Eighteen countries on five different continents were represented. The number of AIH patients treated by the participating physicians ranged from <20 in 2 (5%) to >200 in 17 (46%). Twenty-five respondents (68%) had >20 years of experience and 24 (65%) were active in a transplant centre. There were no differences in terms of number of AIH patients or years of experience between respondents working at a transplant vs. nontransplant centres. Table 1 summarises the characteristics of respondents.

Induction therapy

Thirty-three participants reported commencing induction therapy in a patient with acute AIH and a weight of 75 kg with predniso(lo)ne in isolation. The preferred daily dose of predniso(lo)ne differed markedly among participants [20 mg: $n = 1$, 30 mg: $n = 1$, 40 mg: $n = 15$, 60 mg: 12, 75 mg (1 mg/kg): $n = 3$ and 100 mg: $n = 1$]. Three participants reported to start with predniso(lo)ne 30 mg/day and simultaneously add azathioprine (AZA) at 1 mg/kg/day, whereas another reported to start with predniso(lo)ne 75 mg/day and mycophenolate mofetil 1 g twice per day. Thirty-six participants would taper prednisolone dose over the next 3 months to minimal possible dose ($n = 25$) or a daily dose of 10 mg/day ($n = 1$). Of note, none of the participants reported the use of budesonide as a first-line induction agent for the acute presentation of AIH. The majority ($n = 32$) would subsequently introduce AZA maintenance therapy ($n = 22$) while tapering steroids ($n = 10$) commencing this strategy between 2 and 10 weeks after initiation of induction therapy. Only five (14%) participants reported the routine use of thiopurine S-methyltransferase measurements before starting thiopurine therapy. However, 13 (35%) participants monitored compliance by measuring 6-thioguaninenucleotide levels. Fourteen (38%) perform routine measurements of autoantibody titres during follow-up.

Treatment withdrawal

Thirteen (35%) participants reported that they routinely perform a liver biopsy at 2 years of stable biochemical remission. In the presented case (Case 1), 14 participants

Table 1 | Characteristics of respondents

Country	Years in practice	Number of AIH patients	Transplant centre
Australia	>20	<20	No
Austria	10–20	>200	Yes
Brazil	>20	>200	Yes
Canada	5–10	100–200	Yes
Canada	>20	>200	No
China	10-20	>200	Yes
France	>20	100–200	Yes
Germany	5–10	50–100	Yes
Germany	>20	>200	Yes
Germany	10–20	>200	Yes
Germany	>20	20–50	Yes
Germany	>20	>200	Yes
Greece	>20	>200	No
Iceland	>20	20–50	No
Italy	10–20	20–50	Yes
Italy	>20	100–200	Yes
Italy	10–20	>200	Yes
Italy	>20	>200	Yes
Italy	>20	100–200	No
Japan	>20	>200	No
The Netherlands	>20	100–200	Yes
The Netherlands	5–10	50–100	No
The Netherlands	5–10	100–200	No
The Netherlands	>20	100–200	No
The Netherlands	>20	50–100	Yes
Poland	>20	100–200	Yes
Portugal	>20	50–100	No
Spain	>20	100–200	Yes
Spain	>20	100–200	Yes
Spain	>20	50–100	No
Switzerland	10–20	<20	No
United Kingdom	5–10	>200	Yes
United Kingdom	>20	>200	Yes
United Kingdom	>20	>200	Yes
United Kingdom	>20	100–200	No
United States	<5	>200	Yes
United States	>20	100–200	Yes

(38%) would have performed liver biopsy when the patient was in stable biochemical remission. If histological inflammation and severe fibrosis or cirrhosis are absent in a 2-year treatment evaluation biopsy, four (11%) participants would attempt reduction of AZA, whereas 10 (27%) attempt withdrawal altogether.

Other consideration regarding management

Twenty-nine participants (78%) reported that they routinely use Fibroscan (Echosens, Paris, France) for non-invasive assessment of fibrosis during follow-up of their patients. Twenty-five participants (68%) routinely perform DEXA scan to check for the development of

osteoporosis during follow-up. A minority of respondents ($n = 14$, 38%) perform routine measurements of auto-antibody titres during follow-up.

Second-line therapy in nonresponse and intolerance

The respondents were asked to provide the approximate number of patients that were treated with six medications that are considered as second-line therapy by society guidelines. Overall, the large majority of hepatologists ($n = 31$) reported to have any experience with second-line medication in the management of AIH. Mycophenolate mofetil is the most widely used second-line agent ($n = \sim450$, 28 centres). Tacrolimus ($n = \sim115$, 21 centres) and ciclosporin ($n = \sim112$, 18 centres) are less often reported. One centre reported experience with infliximab ($n = 12$). Rescue therapy with rituximab has been attempted (but not published) in seven centres ($n = \sim22$). Most of the experience with second-line therapy using ciclosporin and tacrolimus resides in the larger tertiary referral centres with a transplant programme, but these agents are also used in small numbers in non-transplant centres (Figure 1).

Liver transplantation and immune suppression

In two cases, the 44-year-old man with intolerance to standard therapy requiring second-line therapy (Case 3) and a 25-year-old woman with acute liver failure due to AIH (Case 4), the respondents were asked about the assessment and/or referral for liver transplantation. Case 3 continued to have severe liver biochemical abnormalities with sign of deteriorating liver function tests (INR 1.4. Albumin was 32 g/L) 6 months after tacrolimus (4 mg/day) was added while maintaining prednisolone 20 mg/day and mycophenolate mofetil 2 g/day. Twenty-three respondents said they would assess the patient for liver transplantation, whereas nine answered that they would maintain the current regimen ($n = 3$) or consider alternative immunosuppressive therapy ($n = 6$). Of these 23 respondents, 11 answered that they would maintain the current immunosuppressive regimen, whereas seven opted for reducing immunosuppression in preparation of liver transplantation. Five respondents chose to the therapeutic option of Infliximab or rituximab salvage therapy while assessing the patient for liver transplantation.

Case 4 presented with acute onset of jaundice, had a model for end-stage liver disease score of 23 [ALT 2700, AST 2103, AP 146 IU/L, total bilirubin 237 μmol/L (13.8 mg/dL) and albumin levels of 2.9 g/dL, INR 1.6] and a liver biopsy showing 'complete collapse of the parenchyma'. Twenty-nine respondents would start induction therapy with predniso(lo)ne with ($n = 4$) or without ($n = 25$) AZA. Nine respondents would refer the patient immediately for liver transplantation, only one of which would avoid treating the patient with any immunosuppressant. In this phase, the reported choice of induction therapy mostly consisted of high-dose steroid therapy with either predniso(lo)ne 1 mg/kg/day ($n = 11$), methylprednisolone intraveneously 1 g/day for 3 days ($n = 9$), 60 mg prednisolone/day ($n = 2$), 100 mg prednisolone/day ($n = 2$) or methylprednisolone IV 100 mg/day for 7 days ($n = 1$). Upon further deterioration despite the institution of immunosuppressive therapy, 21 respondents would have assessed the patient for liver transplantation. The majority of these respondents ($n = 13$) would maintain the immunosuppressive regimen in preparation of transplantation, whereas nine respondents would start to reduce immunosuppression. Thirteen participants (transplant $n = 10$; non-transplant $n = 3$) would immediately list the patient for liver transplantation if encephalopathy was present at that stage.
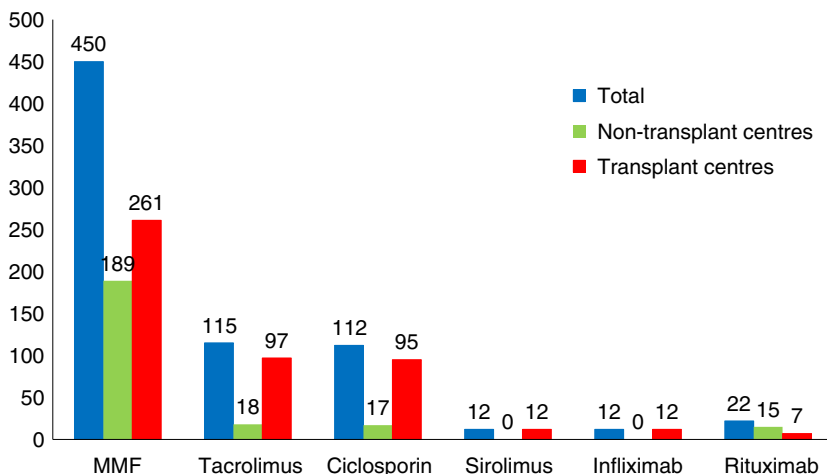

Figure 1 | Reported use of second-line therapies in the management of autoimmune hepatitis. Reported number of patients treated with second-line therapies in the centres of participating physicians.

DISCUSSION

This survey shows that predniso(lo)ne remains the preferred agent for induction of remission in newly diagnosed patients with AIH. Moreover, there is a lack of consensus among expert hepatologists regarding both the initial management and follow-up of patients with AIH. In addition, and despite the lack of good quality evidence, there is considerable experience within the field albeit largely unreported in relation to second- and third-line therapies for difficult-to-treat AIH patients.

All experts surveyed routinely use predniso(lo)ne as initial treatment for AIH, but there is a wide variation in the dose and time that is taken to taper the dose. While a minority of respondents start therapy with a combination of prednisolone and AZA, the majority starts prednisolone in isolation only adding AZA once steroids are being tapered. These strategies reflect the differences regarding combination therapy between the 2010 American Association for the Study of the Liver guidelines and the 2015 European Association for the Study of the Liver guidelines; while the American Association for the Study of the Liver guideline recommends starting either a fixed dose of 50 mg/day or 1–2 mg/kg/day of AZA at the same time as steroids,[12] European Association for the Study of the Liver recommends 1–2 mg/kg/day of AZA to be started only 2 weeks after the introduction of steroids.[14] Whether one strategy has an advantage over the other is unknown, since studies addressing this question are currently not available. Interestingly, none of the respondents reported the use of budesonide as a first-line agent for induction of remission despite their inclusion as a therapeutic option in treatment naïve patients in both British and European guidelines and the presence of randomised data in noncirrhotic patients.[16]

Once remission (defined as normalisation of ALT, IgG levels as well as the absence of inflammatory activity in liver biopsy) is attained, AZA, either as monotherapy (European Association for the Study of the Liver guideline) or in combination with steroids (European Association for the Study of the Liver, American Association for the Study of the Liver and British Society for Gastroenterology guidelines), remains the preferred strategy for its maintenance. This is in line with a systematic review of randomised, controlled trials showing that maintenance therapy with AZA alone or in combination with prednisolone was superior to prednisolone monotherapy.[17] Interestingly, the recent budesonide trial, in which patients on the prednisolone arm were switched at 6 months to open-label budesonide, showed that combination of AZA with budesonide maintained remission while reducing the incidence of steroid-specific side effects.[16] Thus, it seems that the role of budesonide in AIH relies more on its efficacy as a maintenance drug in noncirrhotic patients who experience steroid side effects, rather than as a first-line induction agent.

Although lack of response and toxicity are important issues regarding therapy with thiopurines, attempts to optimise treatment response and avoid the potential occurrence of side effects by thiopurine methyltransferase activity assessment or 6-thioguaninenucleotide (and 6-methylmercaptopurine) measurements is only done by a small minority of participants and does not appear to be the standard of care despite recent recommendations regarding the occurrence of cytopaenia (British Society for Gastroenterology guideline) and maintenance therapy with AZA during follow-up (European Association for the Study of the Liver guideline). It has been reported that, in the setting of inflammatory bowel disease, concerns over thiopurines toxicity often lead to cautious dosing strategies, with an impact in the time taken to achieve remission and overall outcome, including a higher risk of patients being started on other medications unnecessarily.[18] In addition, one recent study has shown that thiopurine therapy in inflammatory bowel disease could be optimised and individualised, according to 6-thioguaninenucleotide levels enabling effective treatment decisions and improving clinical outcomes.[19] In AIH, this strategy may also be possible as 6-thioguaninenucleotide levels are also associated with remission and the metabolism of thiopurines may effectively be optimised with allopurinol in intolerant as well as nonresponsive patients.[20, 21] This suggests that strategies that would permit thiopurine dosing personalization beyond weight have the potential to improve outcomes in AIH and require further prospective studies.

Attempts to withdraw treatment in noncirrhotic patients with stable biochemical remission for 2–3 years may be attempted, and maintenance of remission after treatment withdrawal is possible in some patients.[22] Since up to 50% of patients who have attained biochemical remission (i.e. normalisation of AST and IgG levels) still have histological inflammatory activity,[23] a confirmatory follow-up liver biopsy should be considered.[14] In this regard, 35% of the respondents reported to perform a biopsy after remission is attained and before attempting treatment withdrawal. If histological remission is confirmed, then one-third of those participants favour thiopurine dose de-escalation with the remaining two-thirds attempting withdrawal altogether. Although no study comparing these two strategies is available, a

Table 2 | Published experience with second-line therapies in adult patients with autoimmune hepatitis

Drug/strategy	Year	Naïve/ second-line	Number of patients (n)	Design	Outcome (n)	Follow-up	Dose	Severe side-effect*
Thiopurine optimisation								
Allopurinol addition								
Shamma et al.[25]	2013	Second-line	1: AZA-NR	Retrospective	BR	12 months	75% reduced dose of AZA + 100 mg allopurinol	None reported
de Boer et al.[21]	2013	Second-line	8: 3 AZA-INT, 5 AZA-NR	Retrospective	BR at 6 months in 7 of 8	13 months	25–33% of original thiopurine dose + 100 mg allopurinol	One patient stopped due to neuropathy
Mercaptopurine								
Hubener et al.[26]	2016	Second-line	22: 20 AZA-INT, 2 AZA-NR	Retrospective	BR in 15 of 22 (8 complete, 7 partial)	18.5 months	50 mg MP, 100 mg allopurinol	5 discontinued MP: GI symptoms in 4; GI symptoms and leukopenia in 1
MMF								
Richardson et al.[27]	2000	Second-line	7:3 AZA-INT, 4 AZA-NR	Retrospective	BR in 71% at 3 months; HI in all	46 months	1 g twice daily	Leucopenia in 1 requiring dose reduction
Chatur et al.[28]	2005	Second-line	11	Retrospective	BR in 64%	26.5 months	0.5–2 g daily	Leukopenia in 1+ diarrhoea in 1; both resolved after dose reduction
Hlivko et al.[29]	2008	Naïve + second-line	29: 17 naive; 12 second-line (9 AZA-INT, 3 AZA-NR)	Retrospective	BR in 16 of 19	NA	0.5–2 g daily	34% discontinue due to side effects: headache, nausea/vomiting, myalgias
Hennes et al.[30]	2008	Second-line	36: 27 AZA-INT, 9 AZA-NR	Retrospective	BR in 39% (25% in AZA-NR; 57% in AZA-INT)	16 months	1.0–2 g daily	11 experienced GI side effects; 4 had to stop treatment because of them
Sharzehi et al.[31]	2010	Second-line	21: 9 AZA-INT, 12 AZA-NR	Retrospective	BR in all AZA-NR (n = 12), BR in all AZA-INT (n = 9) and CR in 8 at 12 months	12 months	0.5–2 g daily	1 patient discontinued due to GI symptoms
Baven-Pronk et al.[32]	2011	Second-line	45: 23 AZA-INT, 22 AZA-NR	Retrospective	BR in 13% of AZA-NR, BR in 67% of AZA-INT	3–133 months	0.5–3 g daily	6 discontinued due to side effects (mostly due to GI symptoms)
Zachou et al.[33]	2016	Naive	109	Prospective	BR in 83 of 102 at 3 months, successful treatment withdrawal in 30/40 after 24 (2–129) months	72 months	1.5–2 g daily	2 discontinued due to septicaemia; dose reduction in 5 due to leucopenia or infections
Tacrolimus								
van Thiel et al.[34]	1995	Naive	21	Prospective	BR in 80% at 3 months	3 months	0.075 mg/kg	Discrete rise in creatinine

Drug/strategy	Year	Naïve/ second-line	Number of patients (n)	Design	Outcome (n)	Follow-up	Dose	Severe side-effect*
Table 2	(Continued)							
Aqel et al.[35]	2004	Second-line	11 AZA-NR	Retrospective	BR in 10 of 11; HI in 7 of 7	25 months	0.5–2 mg	1 patient with tremors, hypertension, and generalized oedema
Larsen et al.[42]	2007	Second-line	9 AZA-NR	Retrospective	BR and HI in all	18 months	2–4 mg	No major side effects
Tannous et al.[36]	2011	Second-line	13	Retrospective	BR in 12 of 13	1 to 65 months	2–6 mg	1 HUS at 4 weeks; 1 squamous oral carcinoma at 12 months
Than et al.[37]	2016	Second-line	17: 1 AZA-INT, 16 AZA-NR	Retrospective	BR in most *	60 months	0.5–5 mg	2 noncompliance; 2 abdominal pain, headache, tremor and vomiting; 2 diagnoses of overlap syndrome (1 PSC; 1 PBC); 1 liver transplantation.
Ciclosporin								
Fernandes et al.[38]	1999	Second-line	5 AZA-NR	Retrospective	BR in 4 of 5 at 3 months	27 months	3–5 mg/kg/day	No major side effects
Malekzadeh et al.[39]	2001	Naïve + second line	19: 9 naive, 10 second-line	Prospective	BR and HI in 79%	26 months	2–5 mg/kg/day	1 uncontrolled hypertension at week 8; 1 elevation of liver enzymes at week 18; 1 bloody diarrhoea at week 6. Overall 4 discontinued due to side effects
Infliximab								
Weiler-Normann et al.[40]	2013	Second-line	11 AZA-NR	Retrospective	BR in all, CR in 8 of 11, HI in 5 of 5	6 to > 40 infusions	5 mg/kg at 0, 2, 6 and then after every 4 to 8 weeks	3 discontinued; 2 due to side effects: pneumonia, allergic reaction
Rituximab								
Burak et al.[41]	2013	Second-line	6 AZA-NR	Prospective	BR in all at 24 weeks	72 weeks	1000 mg at days 0 and 15	None reported

MP, mercaptopurine; AZA-NR, azathioprine nonresponse; AZA-INT, azathioprine intolerance; BR, biochemical response; CR, complete biochemical response; GI, gastrointestinal; HI, histological improvement; HUS, hemolytic uremic syndrome; MMF, mycophenolate mofetil, NA, not available; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

* Reported side-effects requiring dose-reduction or discontinuation of the drug.

recent multicenter study including 131 patients in whom treatment was discontinued showed a relapse rate of over 80% within 3 years, reinforcing the notion that the majority of patients require long-term, if not lifelong, maintenance therapy.[24]

For patients who fail to achieve remission on standard immunosuppression, proposed alternative therapies are based on scarce published data, mainly in the form of case reports or small case series (Table 2).[21, 25–42] Nevertheless, this study shows that among experts there is now ample experience with second-line agents, in particular with mycophenolate mofetil. Although patient with insufficient or no response to AZA typically do not respond satisfactorily to mycophenolate mofetil, the reported

Table 3 | Research agenda

To develop standard definitions for endpoints for clinical trials in autoimmune hepatitis (response, nonresponse and remission).

To identify the optimal therapeutic induction scheme in acute vs. chronic autoimmune hepatitis presentations.

To develop alternative first-line maintenance strategies (e.g. mycophenolate mofetil in the CAMARO trial).

To develop alternative second-line maintenance/induction strategies in patients who are nonresponsive to standard therapy (e.g. tacrolimus).

To develop better clinical predictors or biomarkers of patient outcomes (mortality, liver transplant).

remission rates in patients who respond, but are intolerant to AZA, are 60–80%,[30–32] a trend that is reflected by this survey. In addition, it was recently suggested in a prospective real-world study that mycophenolate mofetil may also be an effective first-line alternative agent in AIH,[33] but currently there is no head-to-head comparison with AZA as a first-line maintenance agent. The experience with calcineurin-inhibition, immunosuppressive agents used in organ transplantation mainly resides within the liver transplant centres. Taken together, the data suggest that patients who are AZA intolerant and therefore are candidates for mycophenolate mofetil as second-line can still be managed at tertiary nontransplant centres, while for those who do not respond with improvement of enzyme levels and model for end-stage liver disease score scores even after high-dose steroid induction (up to prednisone 100 mg/day) a second opinion regarding their management should be sought at a transplant centre (European Association for the Study of the Liver, American Association for the Study of the Liver and British Society for Gastroenterology guidelines). Despite recently published guidelines, there are great differences in the management of AIH patients, which emphasises the need for standardised definitions for therapeutic endpoints as well as new prospective (preferably randomised) studies (Table 3).[43, 44]

In conclusion, this study shows that there is a wide variation in the management of patients with AIH even among the most expert in the field, particularly concerning difficult-to-treat patients, possibly reflecting the poor quality of evidence available at the moment, and despite the published guidelines. Future prospective studies should address these issues, and for which transnational collaborations are urgently needed, so that we move from an expert- to an evidence- and personalised-based care in AIH (Table 3).

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Clinical management of autoimmune hepatitis.

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APPENDIX 1
AUTHOR'S COMPLETE AFFILIATIONS

R. Liberal, Institute of Liver Studies, King´s College London, London, UK; Y. S. de Boer, Department of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands; R. J. Andrade, Unidad de Hepatología y Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain; G. Bouma, Department of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands; G. N. Dalekos, Department of Medicine and Research Laboratory of Internal Medicine, School of Medicine, University of Thessaly, Larissa, Greece; A. Floreani, Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy; D. Gleeson, Liver Unit, Royal Hallamshire Hospital, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK; G. M. Hirschfield, Centre for Liver Research, NIHR Biomedical Research Unit, University of Birmingham, Birmingham, UK; P. Invernizzi, Program for Autoimmune Liver Diseases, International Center for Digestive Health, Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; M. Lenzi, Centro per lo Studio e la Cura delle Malattie Autoimmuni del Fegato e delle Vie Biliari, Bologna, Italy and Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Alma Mater Studiorum - Università di Bologna, Bologna, Italy; A. Lohse, University Medical Centre Eppendorf, Hamburg, Germany; G. Macedo, Gastroenterology and Hepatology Department, São João Hospital, Porto, Portugal; P. Milkiewicz, Liver & Internal Medicine Unit, Department of General, Transplant & Liver Surgery, Medical University of Warsaw, Warsaw, Poland; B. Terziroli Service of Hepatology, Clinica Moncucco, Lugano, Switzerland; B. van Hoek, Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands; J. Vierling, Departments of Medicine and Surgery, Baylor St Luke's Liver Center, Baylor College of Medicine, Houston, TX, USA; M. A. Heneghan, Institute of Liver Studies, King´s College London, London, UK

APPENDIX 2
FULL LIST OF INTERNATIONAL AUTOIMMUNE HEPATITIS GROUP CONTRIBUTORS BY RESPONSE

A. Pares, A. J. Montano-Loza, A. Granito, A. E. Kremer, A. Floreani, A. W. Lohse, B. van Hoek, B. Terziroli, C. Schramm, C. Lammert, E. L. R. Cancado, E. Bjornsson, F. Lammert, G. N. Dalekos, G. Bouma, G. M. Hirschflield, G. Macedo, H. Hofer, I. Mackay, J. Neuberger, J. M. Vierling, J.P.H. Drenth, C.M.J. van Nieuwkerk, L. Muratori, M. Lenzi, M. Swain, M. Heneghan, M. Zeniya, O. Chazouilleres, P. Gines, P. Invernizzi, P. Milkiewicz, R. J. Andrade, R. Chapman, T. Berg, H. van Buuren, X. Ma.