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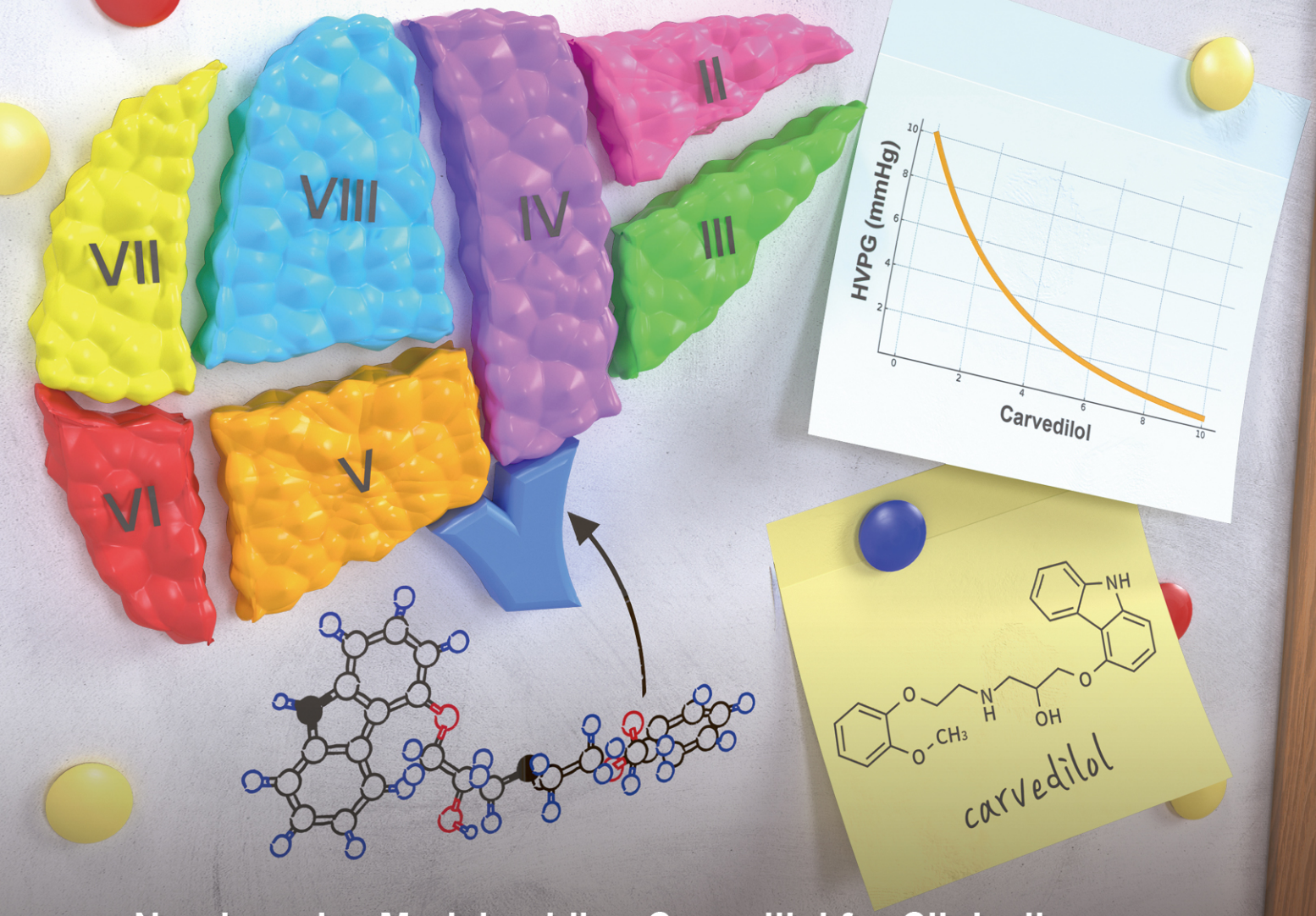

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Review

Hard-to-treat autoimmune hepatitis and primary biliary cholangitis: The dawn of a new era of pharmacological treatment

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Patients with hard-to-treat autoimmune hepatitis (AIH) or primary biliary cholangitis (PBC) are defined *a posteriori* as those who do not show a sufficient response or are intolerant to pharmacological treatments, thus not achieving biochemical surrogate endpoints that are associated with long-term liver-related-event-free survival. The absence of a recently harmonized definition of 'complete biochemical response within 6 months ($CBR_{\leq 6M}$)', which is defined as the normalization of serum transaminase and IgG levels below the upper limit of normal at ≤6 months after treatment initiation, is regarded as hard-to-treat AIH. The implementation of $CBR_{\leq 6M}$, in turn, has been facilitating clinical trials, e.g., between azathioprine and mycophenolate mofetil, to reconsider appropriate first-line steroid sparing agents, leading to a reduction in the number of hard-to-treat AIH cases. Regarding PBC, one of the disseminated definitions of hard-to-treat patients is the absence of POISE criteria, which are evaluated at 12 months with serum alkaline phosphatase and bilirubin levels, after the introduction of ursodeoxycholic acid. Hard-to-treat PBC not meeting the POISE criteria has very recently been the target population for the U.S. FDA-approved second-line drugs, elafibranor and seladelpar. In future pharmacological treatment of AIH and PBC, the primary objective for AIH is likely to focus on lowering the number of hard-to-treat patients with personalized steroid sparing treatment regimens. A challenging goal in PBC treatment is the further optimization of treatment surrogate endpoints, even to the stricter alkaline phosphatase normalization, with which an indication of second- or later-line drugs might be expanded, but could ultimately lengthen patients' long-term survival. **(Clin Mol Hepatol 2025;31:90-104)**

Keywords: Autoimmune hepatitis; Primary biliary cholangitis; Treatment

INTRODUCTION

Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are autoimmune liver diseases (ALDs), and each involves a progressing clinical course without spontaneous cure if left untreated. The goal of pharmacological treatments for ALDs is the prevention of disease progression from liver-related outcomes. Toward this goal, it is necessary to precisely delineate the manifestations of AIH and PBC and to appropriately introduce and modulate pharmacological treatments if necessary, relying on the patients' treatment responses to first-line drugs as determined

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based on surrogate endpoints (ideally within a specified timeframe).[1-8] Following the implementation of a validated marker of treatment response in PBC clinical trials, several second-line drugs became available very recently.[9,10] The definition of treatment response in AIH was also recently updated,[11] providing a path for new clinical trials to address unmet pharmacotherapy needs.

With novel drugs and updated clinical endpoints, we are in the midst of a paradigm shift regarding ALDs treatment strategies. This review makes an appraisal of the definitions of hard-to-treat AIH and PBC and discusses current and future treatment strategies for these diseases, at the dawn of a new era of the pharmacological treatment of ALDs.

AUTOIMMUNE HEPATITIS

Pharmacological treatment for AIH: General considerations

An AIH diagnosis is based on these criteria: (i) histological abnormalities (portal lymphoplasmacytic hepatitis, with more-than-mild interface hepatitis and/or lobular hepatitis);[12] (ii) laboratory findings, i.e., elevated serum transaminases and increased serum immunoglobulin G (IgG); and (iii) positive results of disease-defining autoantibodies, together with (iv) the exclusion of other liver diseases.[1,2,4] AIH has no signature diagnostic features unlike PBC, which has the signature diagnostic feature of the presence of anti-mitochondria antibody (AMA).

Due to AIH's autoimmune nature, immunosuppressive treatment is required. The introduction of corticosteroid (CS) as a core immunosuppressive agent for disease remission and that of azathioprine (AZA) as a first-line steroid-tapering agent for remission maintenance significantly improved the long-term outcomes of AIH patients.[2] Although clinical practice guidelines have recommended the synthetic steroid budesonide (with less systemic adverse effects) as an alternative to prednisolone (PSL) for non-severe acute or chronic AIH,[2] a recent real-world propensity score-weighting multicenter study indicated the inferiority of budesonide to PSL as a first-line drug with regard to biochemical response.[13] PSL and AZA have been a consistently endorsed first-line treatments for AIH for over 20 years.

An observational study at specialized centers in the Netherlands have suggested high effectiveness of CS+AZA, as biochemical remission can be achieved with them in up to 80% of patients.[14] However, the desired time to remission was not prespecified, and results indicated that such percentages are only reached after ≥3 years of treatment. [14] Since the time to remission or to a rapid response to first-line treatment was associated with better long-term outcomes,[15,16] it remains necessary to determine the precise time to remission afforded by first-line treatments for AIH in real-world practice.

Defining hard-to-treat AIH

A treatment response-guided standardized definition of hard-to-treat AIH

In 2022, a consensus of the International Autoimmune Hepatitis Study Group (IAIHG) regarding treatment response criteria and endpoints that encompass a complete biochemical response (CBR), insufficient/non-response, remission, and intolerance to AIH treatments was reached by the Delphi approach through a systemic review of the literature concerning AIH patients' treatment responses.[11] A simple and reproducible structure was provided for hepatologists, and the urgent need to not only set a standard for the reporting of study results, but also to enable compari-

Abbreviations:

AASLD, American Association of the Study of Liver Disease; AE, adverse event; AIH, autoimmune hepatitis; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transaminase; ALDs, autoimmune liver diseases; AZA, azathioprine; BAFF-R, B-cell activating factor-receptor; BA, bile acid; BZF, bezafibrate; CBR, complete biochemical response; CS, corticosteroid; CYA, cyclosporine; EMA, European Medicine Agency; ERN RARE-LIVER, European Reference Network on Hepatological Diseases; HAI, hepatitis activity index; FDA, U.S. Food and Drug Administration, FXR, farnesoid X receptor; FGF, fibroblast growth factor; HRQOL, health-related quality of life; HSC, hepatic stellate cells; HR, hazard ratio; IAIHG, International Autoimmune Hepatitis Study Group; IBAT, ileum bile acid transporter; IgG, immunoglobulin G; ITT, intention-to-treat; JPBCSG, Japanese Primary Biliary Cholangitis Study group; LLN, lower limit of normal; LSMs, liver stiffness measures; LDAA, low-dose azathioprine-allopurinol co-therapy; LT, liver transplantation; MMF, mycophenolate mofetil; NOX, nicotinamide adenine dinucleotide phosphate oxidases; NTT, number needed to treat; NRS, numerical rating scale; OR, odds ratio; OCA, obeticholic acid; PROs, patient-reported outcomes; PPAR, peroxisome proliferator activator receptor; PSL, prednisolone; PBC, primary biliary cholangitis; RCT, randomized-controlled trial; 6-MP, 6-mercaptoprine; SOC, standard of care; TAC, tacrolimus; TB, total bilirubin; TGN, thioguanine nucleotide; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

sons of real-world data obtained in observational clinical studies was described.

CBR was defined in the IAIHG consensus as the normalization of the serum levels of transaminases and IgG below the upper limit of normal (ULN) by ≤6 months after treatment initiation (hereafter, '$CBR_{\leq 6M}$'),[11] and the lack of a CBR was defined as an insufficient response. Non-response was evaluated based on the treatment response within 4 weeks after treatment initiation: a <50% decrease in transaminases.[11] Treatment intolerance was defined as any adverse events (AEs) possibly related to treatment, leading to potential treatment cessation.[11] CBR and non-response were externally validated for their association with liver-related endpoints (liver transplantation [LT] or liver-related death) using the data from a multicenter retrospective cohort (n=404); $CBR_{\leq 6M}$ was associated with less frequent liver-related endpoints (0% vs. 7.5% in non-CBR; log-rank *P*=0.003), and non-response was associated with significantly more frequent liver-related endpoints (21.4% vs. 2.4% in responders; log-rank *P*<0.001). The consensus recommended that remission should be determined pathologically based on a hepatitis activity index (HAI) value <4/18 points.[11]

The IAIHG consensus is remarkable, as it sets and advocates a time point at which patients' treatment response should be evaluated (i.e., at 6 months); a lack of $CBR_{\leq 6M}$ would be regarded as a standardized core criterion of hard-to-treat AIH. First-line therapies can be reconsidered to achieve $CBR_{\leq 6M}$ as a surrogate treatment endpoint, preventing insufficient responses and intolerance within 6 months of treatment, or even to reduce long-term non-beneficial effects of sustained PSL treatment. This criterion is also applicable as an inclusion criterion for second- or later-line treatment for patients being treated for >6 months.

Although the normalization of serum transaminases and IgG <ULN were likely to be chosen as $CBR_{\leq 6M}$ criteria by the Delphi approach, according to the typical characteristics of AIH serum biochemistry, the robustness of the definition of $CBR_{\leq 6M}$ should be a matter of debate,[17-19] although the definition was externally validated in the consensus report. A Canadian multicenter cohort study assessed the clinical data of 609 AIH patients over time to evaluate the associations between the trajectories of biochemical parameters and clinical event-free survival.[19] Prolonged elevations of alanine transaminase (ALT) (hazard ratio [HR] 1.07; 95% CI 1.00–1.13) and aspartate transaminase (AST) (HR 1.13; 95% CI 1.06–1.21) were associated with a higher risk of clinical events; IgG was not. A study of 301 patients with type 1 AIH by the Dutch Autoimmune Hepatitis Study Group did not identify IgG in the first 12 months of treatment as a predictive factor for survival.[18] Moreover, in real-world practice, not all AIH patients present with elevated IgG.[20]

The question of whether the definition of CBR that includes IgG is unnecessarily stringent for the prediction of long-term outcomes is of concern. It is also possible that the two retrospective and contradicting cohort studies cited above may lack enough power to validate IgG as a predictive factor. The IAIHG registry (which includes the cases of 1,700 patients with a 10-year median follow-up) very recently validated the lack of a $CBR_{\leq 6M}$ as an independent prognostic risk factor for poor outcomes (HR 5.7; 95% CI 3.4–9.6).[21] Regarding the prognosis according to disease stage, $CBR_{\leq 6M}$ was associated with increased long-term survival in cirrhotic patients and with a reduced likelihood of progression to cirrhosis in pre-cirrhotic patients. Over 90% of the patients in the IAIHG registry are Caucasian, and a Chinese single-center study confirmed that a $CBR_{\leq 6M}$ was associated with better survival in Asian patients with AIH.[22] As of this writing, the IAIHG-endorsed parameter $CBR_{\leq 6M}$ is likely acceptable for daily practice and for future clinical research.

Real-world analyses of treatment response in AIH

Before the IAIHG declaration of AIH treatment response criteria of AIH, a prospective multicenter study of 231 AIH patients enrolled in 2017–2022 by the European Reference Network on Hepatological Diseases (ERN RARE-LIVER) evaluated the treatment response criteria during the 1st year of treatment with 16 reported different treatment regimens.[23] CBR was defined as the normalization of serum ALT and IgG <ULN (CBR-ALT/IgG). The percentage of patients who achieved a $CBR_{\leq 6M}$-ALT/IgG post-treatment initiation was only 50%, and that of the patients who achieved a $CBR_{\leq 12M}$-ALT/IgG was increased, but not significantly, to 62%. Only 27% of the patients attained a PSL-free CBR-ALT/IgG within the first year. A change of treatment regimen, mostly due to an intolerance to initial treatment, was applied in 30.4% of the patients at ≤6 months.

With regard to ALT normalization at 6 and/or 12 months

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in the ERN RARE-LIVER study, a multivariate analysis demonstrated that severe fibrosis (odds ratio [OR] 0.38; 95% CI 0.16–0.89; *P*=0.026) and change of treatment at ≤6 months (OR 0.40, 95% CI 0.2–0.86; *P*=0.018) were associated with a lesser likelihood of ALT normalization. Considering the above-described results together, it is necessary to reconsider appropriate first-line therapies to improve the CBR rate, irrespective of the heterogeneous clinical manifestations of AIH at the initial diagnosis.

The group of patients with insufficient response at 12 months (33% of the cohort) in the ERN RARE-LIVER study may have included patients with absolute refractoriness to first-line treatment and delayed ALT responders who could achieve a CBR at a later timepoint; the latter may have been primarily treatment-intolerant cases. The cumulative time spent with elevated AST and ALT, as well as whether CBR had been achieved by month 12, were reported to be significantly associated with clinical event-free survival.[15,16,19] As the IAIHG consensus report did not compare the risk of liver-related endpoints between $CBR_{\leq 6M}$ and $CBR_{\leq 12M}$, the absence of a $CBR_{\leq 12M}$ could be an alternative definition of hard-to-treat AIH,[15,16] depending on the patient context (Table 1).

The risk of a flare or relapse during treatment is another non-negligible and elusive aspect of hard-to-treat AIH. The presence of multiple ALT relapses and flares was recognized as associated with poor long-term outcomes.[24,25]

Treatments for hard-to-treat AIH

Approaches to reduce the risk of hard-to-treat AIH

To improve the probability of a CBR and to reduce intolerance to first-line treatments in the real-world treatment of AIH, a re-evaluation of first-line therapies was recently initiated through an open-label randomized-controlled trial (RCT) of AZA versus mycophenolate mofetil (MMF) for the induction of remission (the CAMARO trial).[26] MMF+PSL achieved a higher rate of the primary endpoint $CBR_{\leq 6M}$-ALT/IgG compared to AZA+PSL as shown by an intention-to-treat (ITT) analysis (56.4% vs. 29.0%: difference, 27.4 percentage points; 95% CI 4.0–46.7; *P*=0.022). As AZA usage was associated with treatment intolerance with more AEs than MMF, resulting in treatment cessation (25.8% vs. 5.1%; *P*=0.0188), the difference in these drugs' tolerability profiles was likely the primary reason for the difference in the achievability of the primary endpoint (ITT).

Although a meta-analysis revealed that the combination of MMF+CS was the most widely prescribed second-line treatment (providing histological remission in many patients),[2] MMF is still an off-label drug for AIH. It is not known whether MMF as a first-line treatment is associated with higher rates of sustained CBR compared to AZA after longer follow-ups. In this regard, the personalized optimization of AZA efficacy to prevent insufficient response, relapse, and intolerance remains a significant challenge.

A single-center retrospective matched cohort study comparing the use/non-use of the metabolite monitoring of thioguanine nucleotide (TGN) as an active metabolite of AZA during the treatment of weight-based AZA dosing obtained several interesting findings.[27] First, a sustained biological normalization (BR)-AST/ALT/globulin at 6 months of treatment was superior in the patient group with TGN monitoring compared to those without it (77% vs. 60%, *P*=0.008), although referral bias probably existed in the

Table 1. Complete Biochemical Response in AIH at month 6 or 12

Definition	Usages	Limitations
$CBR_{\leq 6M}$	✓ Daily clinical practice (for patients excluding intolerant to first-line steroid sparing agents) ✓ A standard for the reporting study results[11] (including comparative effectiveness study) ✓ Surrogate endpoint for clinical trials of first-line steroid sparing agents[26] ✓ Absence of $CBR_{\leq 6M}$ as an inclusion criteria for clinical trials of second-line steroid sparing agents[30]	✓ Overestimation of inadequate response? (No direct comparison to$CBR_{\leq 12M}$[11])
$CBR_{\leq 12M}$	✓ Daily clinical practice (for patients including intolerant to first-line steroid sparing agents) ✓ Absence of $CBR_{\leq 12M}$ as an inclusion criteria for clinical trials of second-line steroid sparing agents	✓ Underestimation of inadequate response? (No direct comparison to $CBR_{\leq 6M}$[11])

AIH, autoimmune hepatitis; CBR, complete biochemical response.

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sense that the patients with TGN monitoring likely had more-severe disease or a hard-to-treat background at study entry, demonstrated by their higher PSL doses and the number of patients on double/triple immunosuppression. Second, among the patients with TGN monitoring, those with a sustained BR had significantly more frequently exhibited TGN levels within the therapeutic range of 225–450 pmol/8×10^8 erythrocytes than those who failed to achieve or lost a BR (40% vs. 13%; *P*<0.0001). Third, with regard to subtherapeutic TGN levels, the patients with the lowest levels (<75 pmol/8×10^8 erythrocytes) had higher transaminase levels than the patients within the therapeutic range, while the intermediate subtherapeutic TGN range (75–225 pmol/8×10^8 erythrocytes) was associated with fewer drug-related AEs but was without a significant reduction in the BR rate.

A recent multicenter study (led by the ERN RARE-LIVER) of AIH patients treated with AZA confirmed the value of sequential 4-year TGN monitoring.[28] The patients with a stable CBR showed significantly higher average TGN levels compared to those failing to maintain a CBR (260 vs. 181 pmol/0.2 mL; *P*=0.0014) or never achieving a CBR (260 vs. 153 pmol/0.2 mL; *P*<0.0001). Prospective studies to evaluate the predictive value of early TGN monitoring for $CBR_{\leq 6M}$ are warranted.

Modulation of first-line treatments with AZA and related drugs

In cases of suspected AZA intolerance with AE manifestation within the first few weeks of treatment, an attempt to restart from a low dose of 6-mercaptoprine (6-MP, the first metabolite of AZA) is generally recommended, as it is tolerated in up to half of such patients.[29] As low-dose azathioprine-allopurinol co-therapy (LDAA) has been effective against inflammatory bowel disease, the above-mentioned ERN RARE-LIVER study evaluated the effect of adding allopurinol to thiopurines for patients with hard-to-treat AIH (n=36).[28] This co-therapy increased the median 6-TGN level from 168 pmol/0.2 mL in AZA monotherapy to 321 pmol/0.2 mL (*P*<0.0001), while it lowered the level of 6-MMP, a metabolite associated with toxicity, from 2,125 to 84 pmol/0.2 mL (*P*<0.0001), resulting in improved transaminases in all patients and a long-term CBR in 75%. LDAA and CS could represent efficient alternative first-line treatments for AIH.

Second- to third-line therapies for hard-to-treat AIH

The goal of second-line treatments for AIH is the achievement of an eventual CBR in patients who did not meet $CBR_{\leq 6M}$ or $CBR_{\leq 12M}$. Second-line therapies have been anecdotally performed with MMF, calcineurin inhibitors (cyclosporin A [CYA] or tacrolimus [TAC]), or biologics (e.g., infliximab). In 2020, the American Association for the Study of Liver Diseases (AASLD) conditionally recommended (after a systematic review) with low certainty the use of MMP or TAC to achieve and maintain the biochemical remission of AIH.[2] The ongoing TAILOR study, an open-label phase IIIb RCT (NCT05221411) comparing the effectiveness and safety of TAC and MMF as second-line treatments for AIH patients (n=86) who failed to reach $CBR_{\leq 6M}$, has the primary endpoint $CBR_{\leq 12M}$ after the introduction of TAC or MMF.[30] That study is the first RCT evaluating second-line treatments of hard-to-treat AIH in the $CBR_{\leq 6M}$ era.

The future of hard-to-treat AIH: Pharmacological therapies in development and beyond

Several emerging drugs, the mechanisms of which are distinct and have different targets of immunomodulation, are in development. Zetomipzomib, a first-in-class small-molecule selective immunoproteasome inhibitor, is being investigated in a double-blind phase IIa RCT in patients with hard-to-treat AIH (insufficient response even after 3 months of first-line treatment or relapse after BR) (PORTOLA; NCT05569759).

B cell-targeted therapy has been gaining attention for years. The efficacy of ianalumab (development code VAY736), a monoclonal antibody against B cell-activating factor-receptor (BAFF-R), is being investigated in a double-blind dose-ranging phase II/III RCT of patients with hard-to-treat AIH without a complete response defined by the AASLD guideline (normalization of AST/ALT/IgG) or intolerance to standard-of-care (SOC, i.e., PSL and AZA) treatment (AMBER; NCT03217422). Ianalumab exerts dual action against pathologic B cells via antibody-dependent cellular cytotoxicity (B-cell depletion) and by blocking BAFF-R-dependent B-cell maturation/survival. Since ianalumab is the long-awaited first biological agent that meets the primary clinical endpoints in the treatment of primary Sjogren's syndrome,[31] we are anticipating promising results for hard-to-treat AIH.

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The efficacy of rituximab, a classical B-cell depletion therapy, was also reported in a multicenter retrospective registry (n=35) among refractory AIH patients and those with concomitant autoimmune or hematological disorders; the rate of CBR after a median duration of 8 months from the first dose exceeded over 80 %, although the free-of-flare rate was 73% at the 2nd year.[32] In addition, a small-molecule, long-acting toll-like receptor 4 antagonist, JKB-122, has been evaluated in a double-blind dose-ranging phase IIb study for its ability to enhance SOC to reach $CBR_{\leq 6M, \leq 12M,}$ and $_{\leq 24M}$ (NCT04371718).

With the recognition of hard-to-treat AIH with common definitions, we hepatologists should be more practically strategic for the personalized realization of both clinical and patient-reported treatment outcomes. First, even though there is a substantial number of patients without $CBR_{\leq 6M}$, would such "hard-to-treat AIH" patients all be regarded as candidates for second-line treatment? As the number needed to treat (NNT) for long-term outcomes would vary due to the heterogenous clinical presentations of AIH, assistance with noninvasive monitoring for the staging of AIH livers, such as liver stiffness measures (LSMs),[33,34] could enable hepatologists to personalize decision-making regarding the indications for second-line treatment, with regard to the benefit/harm balance.

We also need to modulate first- and later-line treatments according to patient preferences and their reported outcomes to improve and ensure patients' health-related quality of life (HRQOL) and life expectancy. MMF has downsides, including a higher cost than AZA and its prohibition in women wishing to become pregnant.[2] The conversion of a maintenance agent and even a complete cessation of drug therapy in hard-to-treat AIH patients after the achievement of a CBR could be the focus of future clinical trials, with HRQOL as a secondary endpoint.

PRIMARY BILIARY CHOLANGITIS

Pharmacological treatment for PBC: General considerations

Primary biliary cholangitis (PBC) is an inflammatory cholestatic bile duct disease that affects primarily interlobular cholangiocytes. Without an early diagnosis and subsequent pharmacological intervention with ursodeoxycholic acid (UDCA), cholestasis in the hepatic lobules induces secondary damage to hepatocytes and the deformity of lobular architecture, which may give rise to eventual progression to liver cirrhosis and liver failure.[8] PBC is characterized by a specific diagnostic signature: the presence of anti-mitochondria antibody (AMA) against mitochondrial pyruvate dehydrogenase complex E2. In the presence of (1) AMA-specific (~90% of cases) or PBC-specific antinuclear antibodies (10–20% of cases with anti-sp100 and/or -gp210 antibody), the diagnosis is achieved with laboratory and pathological findings, i.e., (2) elevated serum cholestatic enzymes (alkaline phosphatase [ALP] and γ-GTP) and (3) injury of intralobular bile ducts (chronic nonsuppurative destructive cholangitis and/or bile duct loss), respectively.[5-7] Clinical guidelines also recommend a serological diagnosis (1+2), even without a pathological examination.[5-7]

Although PBC is a disorder in which autoreactive T cell-mediated cell injury against bile ducts presumably operates under a genetic predisposition and environmental trigger(s),[8] choleretics (e.g., UDCA) and not immunosuppressive agents are needed as the first-line treatment for disease control to prevent poor liver-related outcomes. The introduction of the prototypic choleretic UDCA in the late 1980s dramatically improved the long-term outcomes of PBC.[8] The transformed disease landscape likely led to the change of disease nomenclature from primary biliary cirrhosis to recent cholangitis in 2016.

Treatment with UDCA not only reduces serum cholestatic enzymes as surrogate markers; it also improves liver histology. Using a multicenter international registry of PBC patients and inverse probability treatment weighting, the Global PBC Study Group observed an association between UDCA treatment and a significantly reduced risk of LT-free survival (HR 0.46; 95% CI 0.40–0.52; P<0.001) irrespective of the disease stage and the observed biochemical treatment response.[35] It should be emphasized that the LT-free survival of patients without treatment response to 12 months of 13–15 mg/kg UDCA treatment (based on the GLOBE score) was significantly better than that of the patients without UDCA (HR 0.56; 95% CI 0.45–0.69; P<0.001). The economic advantage of UDCA as an intrinsic secondary hydrophilic bile acid that is chemically synthesized inexpensively, allows its unlimited usage against PBC and has provided guaranted health benefits to pa-

tients over the past several decades. UDCA is the de facto irreplaceable first-line drug for PBC, and its discontinuation is strongly discouraged.[5-7]

Defining hard-to-treat PBC

A treatment response-guided standardized definition of hard-to-treat PBC

Real-world clinical data of PBC patients during UDCA treatment have been retrospectively analyzed to identify factors that are associated with the long-term liver-related event-free survival. Combined usages of these factors should be applicable as binary or quantitative surrogate endpoints of UDCA treatment to estimate treatment responses in clinical research. A wide variety of definitions have been proposed: binary composite criteria including the Barcelona, Paris I/II, Rotterdam, Rochester, Ehime, Nara, Toronto, and POISE criteria.[36-38] The UK-PBC and GLOBE scores are quantitative measures.[38] Most of these are usually determined at 12 months after the initiation of UDCA treatment, and patients who do not fulfill these criteria due to an insufficient response to UDCA are regarded as having hard-to-treat PBC (Table 2).

At around the same time as the emergence of the above definitions, second-line drugs that can be added to UDCA to improve treatment responses were in development. The POISE criterion was introduced as a primary composite endpoint of investigational drugs in recent global RCTs.[9,10,39,40] Evaluations of treatment responses to UDCA at 12 months have become common in real-world hepatology practice, and ALP ≥1.67×ULN is an example used as an indication to add an off-label choleretic drug and in RCTs of investigational drugs.

Real-world analyses of treatment response in PBC

Could long-term outcomes of PBC be extended in individuals who achieve new endpoints by introducing more stringent treatment goals with the updating of surrogate endpoints in pharmacological treatments? If so, which PBC subgroup(s) would gain the longest survival benefit by treatment? Alternatively, should the treatment response be personalized according to patients' disease status? Although we are in the era of U.S. Food and Drug Administration (FDA)-approved second-line drugs, the existing UDCA-alone real-world data should help answer these clinical questions.

The Global PBC Study Group sought to identify serological values that were associated with the longest LT-free survival among patients achieving normalization of the GLOBE score after 12 months of UDCA treatment, i.e., the patients whose long-term survival was predicted to be similar to that of an age-matched healthy population (cohort A).[41] Their analyses demonstrated that the normalization of ALP was associated with the longest LT-free survival.[41] The analyses were extended among the patients who achieved the Paris-II criteria (ALP <1.5×ULN and AST <1.5×ULN and total bilirubin [TB]<1 mg/dL) after 12 month of UDCA treatment (cohort B) to identify serum values that were associ-

Table 2. Definitions of hard-to-treat PBC (Binary)

Definition	Hard-to-treat PBC	Months after starting UDCA
Barcelona[38]	≤40% ALP reduction from baseline and ALP >ULN	12
Paris I[38]	ALP >3 ULN, AST > 2 ULN, or TB >1 mg/dL	12
Paris II[38]	ALP >1.5 ULN, AST >1.5 ULN, or TB >1 mg/dL	12
Rotterdam[38]	TB >ULN and/or albumin <LLN	12
Rochester I[38]	ALP >2×ULN	6
Rochester II[38]	ALP> 2×ULN or TB >1 mg/dL	12
Toronto[38]	ALP >1.67 ULN	24
Nara[37]	GGT>ULN or <69% GGT reduction from baseline	12
Ehime[36]	GGT>ULN or ≤70% GGT reduction from baseline	6
POISE[38,39]	ALP≥1.67×ULN, <15% ALP reduction from baseline and T-Bil >ULN	12

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LLN, lower limit of normal; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, lower limit of normal; PBC, primary biliary cholangitis; GGT, gamma-glutamyl transferase.

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ated with liver-related event-free survival.[42] Liver-related events occurred in 17.0 per 1,000 person-years, and ALP normalization was reproducibly associated with extended survival benefit, i.e., 7.6 months in the 10th year of observation (95% CI 2.7–12.6; *P*=0.003). A subsequent analysis of cohort B was performed to estimate the length of survival benefit to patients with ALP normalization, according to clinical demography: ALP normalization was associated with 52.8 months' longer survival (95% CI 45.7–59.9; *P*<0.001) among the patients aged <62 years and whose LSM values obtained by vibration-controlled transient elastography were ≥10 kPa, whereas it provided only with 1.8-month longer survival (*P*=0.603) among the patients aged >62 and with LSM <10 kPa. Setting the treatment goal higher may not necessarily maximize treatment benefits to all patients; ALP normalization would be a superior surrogate of pharmacological treatment for younger patients with advanced fibrosis stages as evaluated by liver biopsy or noninvasive tests,[43] whereas such a stringent goal may not be needed for older patients at a non-advanced stage. Indeed, the idea of disease stage- and age-dependent preferable treatment goals were suggested from the analysis during first-line UDCA treatment; it could be extrapolated to the scenario after the addition of second-line drugs whose long-term survival benefits have been evaluated in real-world practice.

Treatment for hard-to-treat PBC and their effect on the prognosis

Bezafibrate, the first second-line drug with long-term real-world experience

Peroxisome proliferator activator receptor (PPAR) is a nuclear receptor that modulates diverse metabolic processes including lipid metabolism. Three PPAR isoforms are known: α, γ, and δ. The nonselective agonist bezafibrate (BZF) and the PPARα-selective agonist fenofibrate have long prescription histories for dyslipidemia. An open-label investigator-initiated phase II RCT that identified the add-on potential of BZF to UDCA was conducted in Japan,[44] and since 2000, BZF has been used in Japan as an off-label second-line pharmaceutical for PBC patients who exhibit insufficient biochemical responses to UDCA.

While a 2018 global double-blind phase III RCT using the POISE criteria as the primary endpoint validated the efficacy of BZF for the improvement of biochemical response to UDCA,[40] Japan leads the world in the real-world experience of BZF as a second-line drug for PBC. The Japanese Primary Biliary Cholangitis Study group (JPBCSG) used a Japanese nationwide registry of PBC patients to conduct the first retrospective observational evaluation of the long-term effectiveness of BZF add-on therapy to UDCA (n=746) compared to UDCA alone (n=3,162).[45] Adding BZF to UDCA was associated with (a) decreased all-cause mortality (adjusted HR 0.33; 95% CI 0.19–0.55) and (b) decreased liver-related death or LT (adjusted HR 0.27, 95% CI 0.13–0.57), regardless of age, presence of pruritus, serum biochemistry, or disease stage (both *P*<0.01). Although data regarding treatment responses to BZF were unavailable in that study, BZF should be considered a prototypic second-line drug for PBC, associated with the improvement of long-term outcomes.

Adverse events related to BZF have included rhabdomyolysis, hepatotoxicity, and renal impairment; the risk of renal impairment is the reason for contraindication to patients with advanced chronic kidney disease, but also for disadvantage to long-term usage among older female patients with renal vulnerability. In a study of the treatment of PBC patients with concomitant dyslipidemia, it was reported that BZF could be switched safely and effectively to pemafibrate, a next generation antihyperlipidemic PPAR-α agonist which is excreted primarily by the liver.[46]

Obeticholic acid: The first FDA-approved second-line drug for PBC

In 2016, the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) was approved by the FDA and the European Medicine Agency (EMA) as an add-on second-line drug for patients with inadequate biochemical responses or intolerance to UDCA.[39] Mechanistically, OCA acts mainly on FXR in enterocytes in the ileum, leading to the secretion of fibroblast growth factor19 (FGF19) into the portal blood flow. FGF19 thereafter suppresses CYP7A1 expression in hepatocytes that are downstream from the FGFR4/klotho β signaling pathway, resulting in the reduction of bile acid (BA) synthesis.[38]

The rate of reaching the primary endpoint after 12 months of add-on OCA to UDCA in the global double-blind phase III RCT (the POISE trial) was higher in the 10 mg group (47%) than the placebo group (10%).[39] Durable (≥3-

year) biochemical responses were observed in an open-label extension study,[47] and histological improvement (which included fibrosis composite score reduction) was confirmed in the biopsies of patients at year 3 of OCA treatment.[48] The subsequent multicenter real-world RECAPITULATE study in Italy reported the probability of response (the POISE trial) as 47.2% at year 3; the response in liver cirrhosis was shown to be 34.8% at year 3, which was significantly lower than in non-cirrhosis (P<0.01).[49] Greater transplant-free survival was recently demonstrated among the patients of the POISE trial and open-label extension compared to externally matched hard-to-treat patients from two different registries, i.e., the Global PBC Registry (HR 0.29; 95% CI 0.10–0.83) and the UK-PBC Registry (HR 0.30; 95% CI 0.12–0.75).[50]

Pruritus is a commonly experienced adverse event associated with OCA treatment, as it was occurred in 56%–58% of OCA-prescribed patients in the POISE trial,[39] and hepatic events were also observed in patients at advanced stages. Consequently, since May 26, 2021, FDA has been restricting the use of OCA in patients PBC with advanced cirrhosis; OCA is considered contraindicated for patients in present/past decompensated cirrhosis (Child B or C) and those in compensated cirrhosis with evidence of portal hypertension. A downside of OCA was noted in the EMA recommendation to revoke its conditional marketing approval of OCA, dated June 28, 2024. The decision was made, in particular, due to the inability of a partially enrolled placebo-controlled phase IV trial (the COBALT study) to show improved outcomes in patients treated with OCA, both in the overall population and in a group of early stage.[8]

Emerging PPAR agonists as second-line drugs

The year 2024 has been pivotal for PBC pharmacotherapies. Two PPAR agonists, elafibranor (a PPAR-α/δ agonist) and seladelpar (a PPAR-δ agonist) were granted a rare accelerated approval by the FDA after successful results of double-blind phase III RCTs. Elafibranor 80 mg add-on to UDCA in the ELATIVE trial (NCT04526665) provided a significantly higher rate of meeting the POISE criteria at week 52 versus the placebo group (51.0% vs. 3.8%, P<0.001). Elafibranor also provided a significantly higher rate of ALP normalization versus placebo (15.0% vs. 0%; P=0.002).[10]

In the RESPONSE study (NCT04620733), 61.7% of the patients taking 10 mg seladelpar achieved the POISE criteria at month 12, versus 20.0% of the placebo group (P<0.001); ALP normalization was observed in 25.0% of the seladelpar group and in none of the placebo-treated patients.[9] In the 2-year-long open-label extension study, seladelpar increased the POISE criteria success rate from 66% at month 12 to 79% at month 24.[51] The safety profile of both drugs was favorable.[9,10]

Remarkably, the difference in symptom relief between elafibranor and seladelpar was clear among the patients with moderate-to-severe pruritus as evaluated by the key secondary endpoint: a change in the weekly mean pruritus score on a numerical rating scale (NRS). Seladelpar, but not elafibranor, decreased the NRS significantly compared to placebo (–3.2 vs. –1.7; P<0.005).[9,10]

Two other global RCTs with PPAR agonists are ongoing in phase II or IIb/III trials. The phase II trial is examining pemafibrate with the percentage change in the ALP level at week 12 as the primary endpoint (NCT06247735), and the phase IIb/III trial is investigating the dual PPAR-α/γ agonist saroglitazar with POISE criteria as the primary endpoint (NCT0513336).[52]

Immunosuppressive drugs as investigational second-line drugs

Since PBC is an autoimmune disease, hard-to-treat PBC might encompass subgroups with distinctively high disease activity associated with severe autoimmune reactions and such patients may benefit from immunosuppressants. A double-blind phase III RCT was conducted to analyze the efficacy of 12–16 mg/kg/body weight/day budesonide as a second-line drug for patients at risk of disease progression, defined by criteria including serum ALP >3×ULN at any time since diagnosis and histology (moderate-to-severe periportal or periseptal lymphocytic interface hepatitis or Ludwig stage III fibrosis).[53] Although the primary endpoint, *i.e.*, an improvement of liver histology (grading by HAI score) and no progression of fibrosis was not achieved, a secondary analysis revealed that the proportion of patients who met the POISE criteria was significantly higher in the budesonide group than the placebo group. At month 36, ALP normalization was also observed significantly more often after budesonide treatment (35%) versus placebo treatment (9%; P=0.023). As these results were inconclusive (with an underpowered histological analysis in the sense that only a small number of patients underwent biop-

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sies at year 3), a query arises: could the introduction of alternative noninvasive surrogates of disease grade and stage, such as serum immunological biomarkers and LSM,[43,54] respectively, facilitate future clinical trials of budesonide? The role of immunosuppressants for hard-to-treat PBC remains an open question.

From second-line drugs to future multi-drug combinations

There are still unmet needs for hard-to-treat PBC, despite the embrace of the surge of novel second-line drugs. Treatment with UDCA and second-line drugs beginning at the initial diagnosis of PBC should be considered as a future treatment direction (Fig. 1).

A predictive formula to determine the probability of a biochemical response to UDCA at month 12 was proposed as a UDCA response score, using clinical demography from diagnosis to the start of UDCA treatment, including the values of ALP, ALT, TB, and age.[55] This UDCA response score was associated with the pathological stage evaluated based on the Nakanuma score.[56] The low likelihood of a biochemical response to UDCA is thus attributable to higher disease activity and advanced PBC stage. A futile 1-year observation of the impact of UDCA alone for such prespecified hard-to-treat patients could be avoidable if dual-combination therapies become available for treatment-naïve PBC in the future.

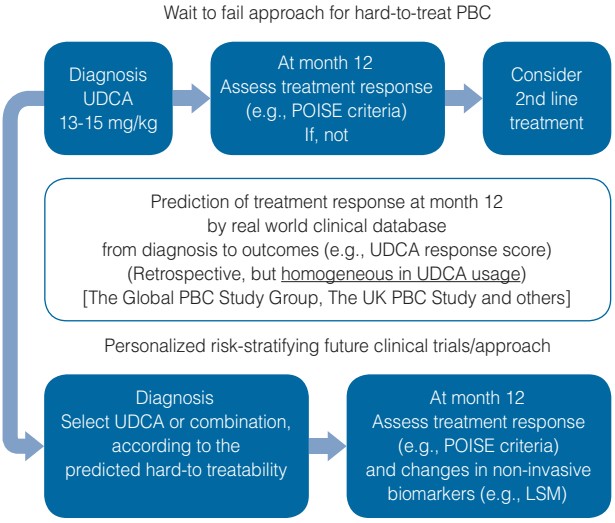

Figure 1. Future treatment strategies for hard-to-treat PBC from the "wait to fail approach" to the "personalized risk-stratifying approach". LSM, liver stiffness measurement; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

A third-line drug in combination with a second-line drug and UDCA is likely to be required for the hardest-to-treat patients who fail to achieve a biochemical response to a second-line treatment. Matsumoto et al. analyzed JPBCSG real-world data and observed that low serum albumin (<3.5 g/dL; HR 7.72; *P*=0.016) and a high TB level (>1.5 mg/dL; HR 14.5; *P*=0.004) were associated with liver-related deaths or LT among patients prescribed BZF+UDCA.[57] A planned interim analysis of a double-blind phase II active-controlled trial with BZF alone and a combination of OCA+BZF revealed that the combination of OCA+BZF 400 mg/day had normalized all five surrogate biomarkers (AST, ALT, TB, ALP, γ-GTP) in 66.7% of patients at week 12.[58] Biochemical remission could be achievable in hard-to-treat PBC with multidrug combinations that induce PPAR and FXR dual activation, probably at a higher rate than with a second-line drug, e.g., PPAR or FXR agonist alone.

Therapies for hard-to-treat PBC (for symptoms)

Two major patient-reported outcomes (PROs) of PBC are fatigue and pruritus, both of which may greatly impair HRQOL.[59] Fatigue and pruritus are very elusive as outcomes in PBC. Fatigue is not associated with disease severity and staging, and even pruritus has shown an inconsistent correlation with serum cholestatic enzymes and staging,[59,60-62] occasionally fluctuating throughout the clinical course of PBC.

The removal of excessive BA (which exerts a systemic pruritogenic effect) from ileo-hepatic circulation through the inhibition of ileum bile acid transporter (IBAT) is a promising approach to the treatment of pruritus in cholestatic liver disease, including PBC.[38] In fact, odevixibat was the first IBAT inhibitor approved for pruritus in patients with progressive familiar intrahepatic cholestasis and Alagille syndrome; double-blind phase III RCTs demonstrated this drug's ability to improve pruritus and reduce serum BA.[63] After a double-blind phase II RCT in which the IBAT inhibitor linerixibat (40 mg twice daily) for 12 weeks significantly improved pruritus,[64] a double-blind phase III RCT (GLISTEN) is ongoing (NCT04950127). Other IBAT inhibitors, including volixibat in a double-blind phase II trial (NCT05050136), are also in development for pruritus. A notable but manageable adverse event is loose stools or

diarrhea that is attributable to pharmacological actions of IBAT inhibitors, *i.e.,* BA-dependent water excretion and increased peristalsis. The nonselective IBT inhibitor elobixibat was approved for constipation treatment in Japan.[65]

Nicotinamide adenine dinucleotide phosphate oxidases (NOX) are enzymes that induce the production of reactive oxygen species. NOX1/4 are expressed in the liver in both non-parenchymal cells, including hepatic stellate cells (HSC), and hepatocytes. During liver injury, with up-regulations of their expression, NOX1/4 may exacerbate liver fibrosis, mainly through HSC activation. Although the patients in a placebo-controlled phase II RCT with the NOX1/4 inhibitor setanaxib as a second-line investigational drug for hard-to-treat PBC did not meet the primary endpoint (the week 24% change in γ-GTP from baseline), the patient-reported secondary endpoint (changes in the mean PBC-40 questionnaire's fatigue domain score) differed significantly between the setanaxib 400 mg twice daily and placebo groups (–9.9% vs. 2.4%; P=0.027).[66] A *post-hoc* analysis demonstrated that absolute reductions in median LSM by week 24 in patients with baseline LSM ≥9.6 kPa treated with setanaxib 400 mg 2×/day was –3.0 kPa (–0.7 kPa for placebo). These results led to investigators to perform a placebo-controlled phase IIb RCT with setanaxib (1,200 or 1,600 mg/day) with hard-to-treat PBC patients with baseline LSM ≥8.8 kPa; ALP reduction was the primary endpoint and was used in combination with the changes in multiple fatigue scores as secondary endpoints (NCT05014672). Fatigue might thus not be the last drug target in patients with hard-to-treat PBC.

Table 3. Pharmacological treatment of (A) AIH and (B) PBC: An update

AIH in adult	
Clinical manifestation at diagnosis	Heterogeneous; acute, chronic, acute on chronic
Surrogate treatment endpoints (For clinical practice and trials)	$CBR_{6M\geq}$ or ($CBR_{12M\geq}$)
Hard-to-treat patients (For clinical practice and trials)	Absence of $CBR_{6M\geq}$ or ($CBR_{12M\geq}$)
First-line treatment (Typical starting dose) Steroid sparing agents* (Typical starting dose)	PSL‡ (20–40 mg daily with AZA, 40–60 mg as monotherapy)† or Budesonide§ (3 mg thrice daily) +AZA‡ (50–100 mg daily)*,† or [6-MP§ (25–50 mg daily)*] +MMF§ (1,000–2,000 mg daily)*
Second-line treatment (Typical starting dose)	+MMF§ (1,000–2,000 mg daily)* +TAC§ (Dose adjusted to trough levels)* +CYA§ (Dose adjusted to trough levels)*

A

PBC	
Clinical manifestation at diagnosis	Homogeneous, albeit wide range of disease activity
Surrogate treatment endpoints (For clinical practice and trials)	POISE criteria (primary) ALP normalization (secondary)
Hard-to-treat patients (For clinical practice and trials)	Unachievable to POISE criteria or ALP normalization
First-line treatment	UDCA‡ (13–15 mg/kg daily)†
Second-line treatment (Typical dose)	OCA‡ (5–10 mg daily)† Elafibnor‡ (80 mg daily) Seladelpar‡ (10 mg daily) Bezafibrate§(200–400 mg daily)† Fenofibrate§(50–150 mg daily)

B

AZA, azathioprine; CBR, complete biochemical response; MMF, mycophenolate mofetil; PSL, prednisolone; 6-MP, 6-mercaptopurine; TAC, tacrolimus; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ALP, alkaline phosphatase.
*See Reference 2 and 29. †With real world outcomes. ‡Approved. §Off-label.

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CONCLUSION

Are we at the dawn of a new era of pharmacological treatment for AIH and PBC? As summarized in Table 3, we have discussed and updated the concepts of treatment endpoints and hard-to-treat patients in this review, with overviews of the spectrum of agents as first- and second-line treatments for AIH and PBC. As it is important to reduce the risk of hard-to-treat AIH in particular by the optimization and personalization of steroid-sparing agents, we need more ambitious clinical trials in the future, following the recent CAMARO trial. Advances in the development of immunomodulators are for immunologically harder-to-treat patients, and progress in the development of non-invasive biomarkers for the prediction of presumably patho-mechanistically distinct subgroup of patients is also warranted.

As for PBC, progress concerning second-line choleretic drugs is evident, but long-term beneficial outcomes of new agent should be estimated in appropriate phase IV trials, against the backdrop of the revocation of OCA. Simultaneously, an appropriate next step is to "set the bar" appropriately, with personalized treatment indications and endpoints, in order to optimize patients' long-term survival with second-line drugs.

Finally, one of the relevant topics not addressed in this review is a distinct group of hard-to-treat patients, namely those with PBC-AIH overlap. No standardized criteria for the diagnosis of PBC-AIH overlap are available, and importantly, the diagnosis of the AIH component itself has been updated with IAIHG's 2022 consensus statement for the histological diagnosis of AIH in which lobular hepatis was adopted as a renewed diagnostic component.[67] Consequently, we are still far from establishing the appropriate indications for the treatment to PBC-AIH overlap, and optimization of the treatment strategy, e.g., either a concomitant use of UDCA and PSL from the initial diagnosis or a sequential add-on to the initial treatment agent, is still a matter of debate.

Using a multifaceted approach, hard-to-treat AIH and PBC should be reappraised in a timely manner until the day that the elimination of pathological autoimmunity in ALDs is achieved for the complete cure of these diseases.

Authors' contributions

A. Komori conceptualized the overall structure of the manuscript. A. Komori and Y. Kugiyama wrote the original draft, followed by the critical review for the manuscript.

Conflicts of Interest

A. Komori received grants as an investigator for clinical trials sponsored by GSK and Kowa Company and speaker and consulting honoraria from GSK and Kowa Company. There is no conflict of interest in Y. Kugiyama.

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