Review

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The search for disease-modifying agents in decompensated cirrhosis: From drug repurposing to drug discovery

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Summary

Patients with decompensated cirrhosis are currently managed through targeted strategies aimed at preventing or treating specific complications. In contrast, a disease-modifying agent should, by definition, be aimed at globally addressing 'decompensated cirrhosis'. To be defined as a disease-modifying agent in decompensated cirrhosis, interventions need to demonstrate an unequivocal benefit on the course of disease in well-designed and adequately powered randomised clinical trials with hard endpoints (*i.e.* patient survival). These trials also need to define the target population, dosage and timing of administration, factors guiding treatment, temporary or permanent stopping rules, transferability to daily clinical practice, cost-effectiveness, and global treatment access. By eliminating the underlying cause of cirrhosis, aetiologic treatments can still influence the course of decompensated disease by halting or slowing down disease progression or even inducing reversion to the compensated state. In contrast, there remains an unmet clinical need for disease-modifying agents which can antagonise key pathophysiological mechanisms of decompensated cirrhosis, such as portal hypertension, gut translocation, circulatory dysfunction, systemic inflammation, and immunological dysfunction. However, in the last few years, the repurposing of "old drugs" that have already been prescribed for more limited indications in hepatology or for other diseases has provided a few candidates, including human albumin, statins, and poorly absorbable oral antibiotics, which are under further evaluation in large-scale randomised clinical trials. New disease-modifying agents are also expected to be identified in the next decade through the systematic repurposing of existing drugs and the development of novel molecules which are currently undergoing pre-clinical or early clinical testing.

Introduction

Every year about 5% to 7% of patients with compensated cirrhosis develop a major complication. This event marks the transition to decompensated cirrhosis, which is often characterised by a tumultuous course and a dramatic shortening of life expectancy unless liver transplantation is performed.[1] The current approach to the management of patients with decompensated cirrhosis is based on strategies targeted at preventing or treating each complication. However, although randomised clinical trials (RCTs) have proven the effectiveness of this approach in managing specific complications, it has only had a small impact on the overall natural history of cirrhosis. In contrast, the concept of a disease-modifying treatment implies that a certain intervention is prescribed to effectively improve the course of the disease independently from the treatment or prevention of a specific complication.[2]

To be defined as a disease-modifying agent in decompensated cirrhosis, the intervention should thus satisfy a series of requirements (Box 1). Since the goal of a disease-modifying agent is to halt or at least slow down the progression of the disease, or even induce recompensation, survival is the primary outcome measure in clinical trials assessing such agents. The incidence of further cirrhosis complications and/or acute-on-chronic liver failure (ACLF) are strongly associated with survival and could be used as surrogate outcome measures to conduct adequately powered studies with more realistic sample sizes. However, these measures would work better as secondary endpoints, which could also include hospitalisations, quality of life, and the cost-effectiveness of treatment.[3,4] To date, very few published RCTs have been designed to address the overall prognosis (as opposed to specific complications) in decompensated cirrhosis. The examples of such studies are the ANSWER, MACTH and ATTIRE trials assessing human albumin[5–7] and the NORFLOCIR trial evaluating norfloxacin.[8] Reliable and conclusive data on disease-modifying agents should thus derive from multicentre, possibly international, well-designed and adequately powered RCTs, emphasising the importance of scientific consortia.

As the term decompensated cirrhosis comprises a heterogeneous population with very different

clinical phenotypes and prognoses,[1,9,10] it is likely that an intervention would only be disease modifying in well-defined subgroups of patients. A typical example is treatment with albumin, which was found to improve the overall prognosis of patients in the ANSWER trial, who presented at enrolment with stable decompensated cirrhosis and persistent grades 2 and 3 uncomplicated ascites,[5] but not of more severely ill patients in the ATTIRE study, who were admitted to hospital for acute decompensation with or without ACLF.[7] It is thus crucial to define the clinical phenotype of the patient subgroups, stratified according to their probability of response to the disease-modifying agent. In addition, the efficacy should ideally not only be confined to a small subgroup of patients because a positive impact on the global burden of the disease represents another important goal of disease-modifying interventions.

To further complicate the scenario, disease-modifying agents may lose their efficacy or even be harmful if the clinical conditions change, as frequently and suddenly occurs in patients with decompensated cirrhosis. Thus, along with the indications for initiating treatment, temporary and permanent stopping rules are also needed.

Finally, other important issues include the transferability to daily clinical practice and access to treatment, dosage and administration schedule, factors guiding treatment, use with other agents to develop combinatorial approaches, and the cost-effectiveness for different healthcare systems worldwide.

The first question is whether disease-modifying agents are already available among the interventions currently used in decompensated cirrhosis. Some aetiological approaches (*i.e.*, antivirals for hepatitis B and C or achieving prolonged abstinence for alcohol use disorders) satisfy most of the requirements described above. It is common experience that eliminating the underlying cause of cirrhosis often influences the course of the disease even in decompensated patients by halting or slowing progression in many cases or even by inducing the reversion to the compensated state in some cases.

Besides eliminating the cause of cirrhosis, to function as a disease-modifying agent, an intervention must affect the underlying pathophysiology of the disease. Unfortunately, in contrast to other chronic pathological conditions, such as inflammatory bowel disease or immune-mediated arthritis, where this type of approach has been routinely used for years,[11,12] an unequivocal pathophysiological disease-modifying treatment endorsed by international guidelines does not yet exist for patients with decompensated cirrhosis.

In the last decade, an increasing understanding of the pathobiology of decompensated cirrhosis [13,14] has revealed new options for targeting key pathophysiological events, such as portal hypertension, bacterial translocation, circulatory dysfunction, systemic and hepatic inflammation, and immunological dysfunction. Due to the complexity of the pathophysiological network in decompensated cirrhosis, with many interacting and often redundant pathways, successful interventions must theoretically act on a single key event – usually located upstream in the pathophysiological cascade – or simultaneously on multiple mechanisms.[2]

Unfortunately, the discovery and clinical development of a new drug is a long process which takes 1-2 decades. Thus, an attractive alternative is drug repurposing or repositioning, which relies on identifying and developing new uses for drugs already on the market.[15] Drug repurposing has many advantages: market-tested drugs have already passed the time-consuming pharmacokinetic, pharmacodynamic, and toxicity profiling evaluation, have proven their safety and efficacy through clinical trials, and have thus been approved by major regulatory agencies for their initially intended application. Consequently, the development time for repurposed drugs can be markedly reduced to even a few years.[15]

The most common approach to drug repurposing involves the selection of candidate drugs based on known targets involved in the pathogenesis of the disease of interest. A typical example was recently provided in patients with compensated cirrhosis by the PREDESCI trial,[16] which tested the efficacy of non-selective beta-blockers (NSBBs). NSBBs are currently recommended for the primary prophylaxis of bleeding in patients with high-risk oesophageal varices based on their capacity to decrease the portal pressure gradient.[17] The results of this double-blind, multicentre RCT demonstrated that in patients with clinically significant portal hypertension, diagnosed as a portal pressure gradient of at least 10 mmHg, NSBBs decreased the risk of first clinical decompensation (mostly represented by ascites), and liver-related death by approximately half. As more than 50% of the patients had only low-risk varices and more than 40% had no varices at all, these findings represent the basis for the repositioning of NSBBs by extending their use to a much wider number of patients with compensated cirrhosis.[16]

In addition to aetiological treatments, this review critically analyses the clinical evidence supporting the use, as disease-modifying agents, of existing treatments that have already been prescribed for more limited indications in decompensated cirrhosis or for other diseases. Lastly, new agents under pre-clinical evaluation or in the early stages of clinical development, which can potentially counteract key mechanisms in the

Box 1. Characteristics of a disease-modifying agent in decompensated cirrhosis.

- Able to modify the course of decompensated cirrhosis
- Efficacy proved by adequately-powered RCTs designed with survival as the preferential primary endpoint (or at least incidence of ACLF and/or sum of complications)
- Identified target populations (subgroup of patients with decompensated cirrhosis for whom a disease-modifying agent is effective or more effective)
- Positive impact on the global burden of the disease
- Established temporary or permanent stopping rules
- Transferability to daily clinical practice
- Able to improve the quality of life of patients
- Cost-effective for healthcare systems
- Safe and well-tolerated

ACLF, acute-on-chronic liver failure; RCT, randomised clinical trial.

Key point

A disease-modifying agent should not prevent or treat a specific complication, but should halt or slow down the progression, or even induce the reversion, of the underlying decompensated state.

pathophysiological network of decompensated cirrhosis, are also discussed.

Aetiological treatments

Treatment for decompensated chronic liver disease includes specific supportive and aetiological interventions. There is emerging evidence that nutritional and exercise interventions can improve a number of elements related to physical frailty and quality of life in patients with chronic liver disease and should therefore be given appropriate consideration.[18,19]

Abstaining from alcohol is critical and has been shown to result in the recompensation of liver disease in many cases and/or the prevention of further clinical deterioration.[20,21] The most effective management strategy is the combination of psychosocial interventions and pharmacological therapy, but the available drug options are greatly limited in decompensated cirrhosis because of the altered liver metabolism and risk of hepatic encephalopathy.[22] Effective interventions to maintain abstinence thus constitute a major unmet clinical need.

For patients with non-alcoholic fatty liver disease (NAFLD), there are no approved therapies and thus the focus is on optimising elements of the metabolic syndrome, such as glycaemic control. Weight loss in relation to decompensated liver disease should be approached with caution as sarcopenia, which is also common with this disease,[23] can be worsened by injudicious weight loss. However, when monitored and in association with lifestyle interventions, weight loss can result in improvements in portal hypertension as well as rendering patients more suitable for liver transplantation.[19] In a recent study, 16 weeks of diet and moderate exercise safely reduced weight by 5 kg and portal pressure (>10% reduction in more than 40% of patients) in overweight/obese patients with cirrhosis (of different aetiologies) and portal hypertension.[24]

For patients with hepatitis C-related decompensated cirrhosis, appropriate antiviral treatment should be considered as there is evidence that improvement or even recompensation can occur in many cases.[25] However, the long-term impact on the complications of the disease and transplant-free survival remains controversial. Patients with severe portal hypertension and a model for end-stage liver disease (MELD) score above a certain threshold, which different studies have located at a score between 15 and 20, seem to be less likely to experience a significant clinical improvement.[26–28] A recent prospective cohort study with a median follow-up of more than 4 years showed that while progression of cirrhosis and death are infrequent, most patients with decompensated cirrhosis and viral clearance exhibit little to no long-term decrease in MELD score, thus remaining at risk of complications and requiring close monitoring.[28] This partial clinical improvement ("MELD purgatory") may negatively affect patients being evaluated for liver transplantation in terms of priority on the waiting list, thus raising the issue of whether to defer antiviral treatment until after transplantation.[29] In addition, the timing of treatment needs to consider the reduced cure rates observed in very advanced disease[30] and should also consider local or national policies concerning the use of HCV-positive organ donors for patients who are HCV RNA-positive or have recently been cured.

If hepatitis B is the cause, then suppressive antiviral therapy should be given immediately as recompensation is possible, particularly in patients with early decompensation.[31] For patients with HBV-related advanced liver failure and for those with liver failure due to concomitant hepatitis D, nucleoside analogues are indicated in anticipation of liver transplantation. In these cases, antiviral treatment is an important element of post-transplant prophylaxis and protection from graft reinfection.[32]

Regarding the other less frequent causes of cirrhosis, there are only sporadic data on the effects of aetiological treatments in patients with decompensated cirrhosis. In relation to autoimmune hepatitis, the priority is to ameliorate the aberrant immune response using several immunosuppressors (*i.e.*, steroids, azathioprine, mycophenolate mofetil, cyclosporine), whilst avoiding the potential increased risk of sepsis and complications.[33] For immune-mediated cholestatic

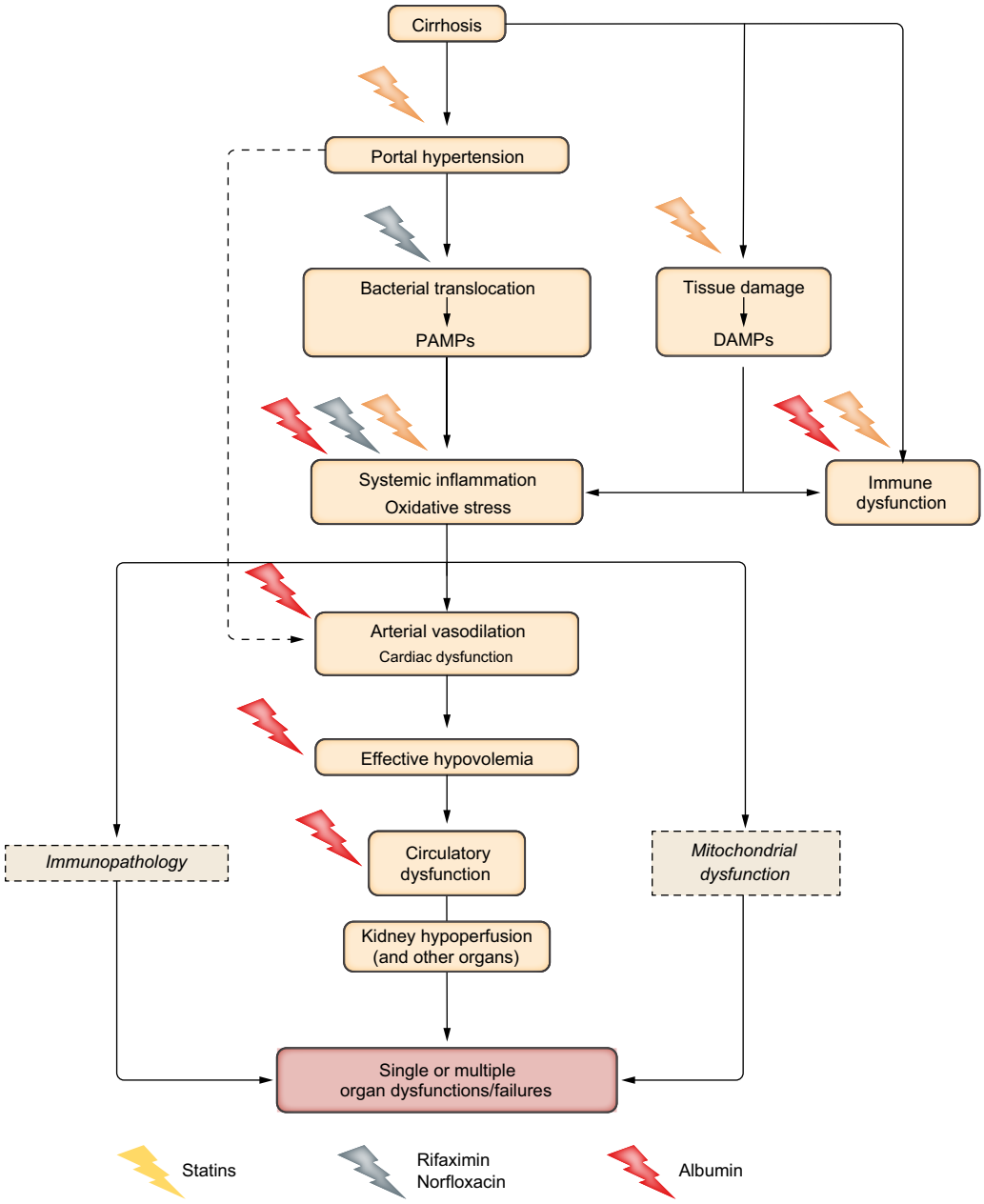

Fig. 1. Targets of action of candidate disease-modifying agents antagonising proposed pathophysiological events in decompensated cirrhosis.

conditions, therapies such as ursodeoxycholic acid and more recently obeticholic acid and bezafibrate will hopefully reduce disease progression and prevent the need for liver transplantation in primary biliary cirrhosis. However, the effectiveness of these drugs, as well as the safety in the case of obeticholic acid and fibrates, have not been proven in patients with decompensated cirrhosis.[34] In contrast, effective therapies for primary sclerosing cholangitis remain a major unmet clinical need.[35] In terms of haemochromatosis, ongoing de-ironing with venesection should be considered with the caveat that concomitant frailty and anaemia may necessitate a more cautious approach. It has been suggested that de-ironing may improve post-transplant outcomes and the

Key point

Improvements in our understanding of the pathobiology of decompensated cirrhosis have revealed new therapeutic approaches to target key pathogenic mechanisms, such as portal hypertension, bacterial translocation, circulatory dysfunction, systemic inflammation, and immunological dysfunction.

Key point

Removing the underlying cause of cirrhosis represents an effective disease-modifying approach. However, a substantial number of patients with decompensated cirrhosis do not benefit from aetiologic treatments (even if successful)

response to sepsis for those on the waiting list,[36] however, in practice, it is seldom undertaken because of concerns around patient frailty.

Pathophysiological treatments

Drug repurposing

In patients with decompensated cirrhosis, attempts to repurpose existing drugs have been made or are under evaluation in large multicentre RCTs. Candidate disease-modifying agents include interventions already prescribed to prevent or treat specific cirrhosis complications, as well as drugs employed in other disease settings. Currently the most promising candidates are poorly absorbable oral antibiotics, simvastatin, and human albumin. A few current interventions antagonise a single well-defined pathogenic event, whereas others simultaneously hit different targets located both upstream and downstream in the pathophysiological cascade of decompensated cirrhosis (Fig. 1).

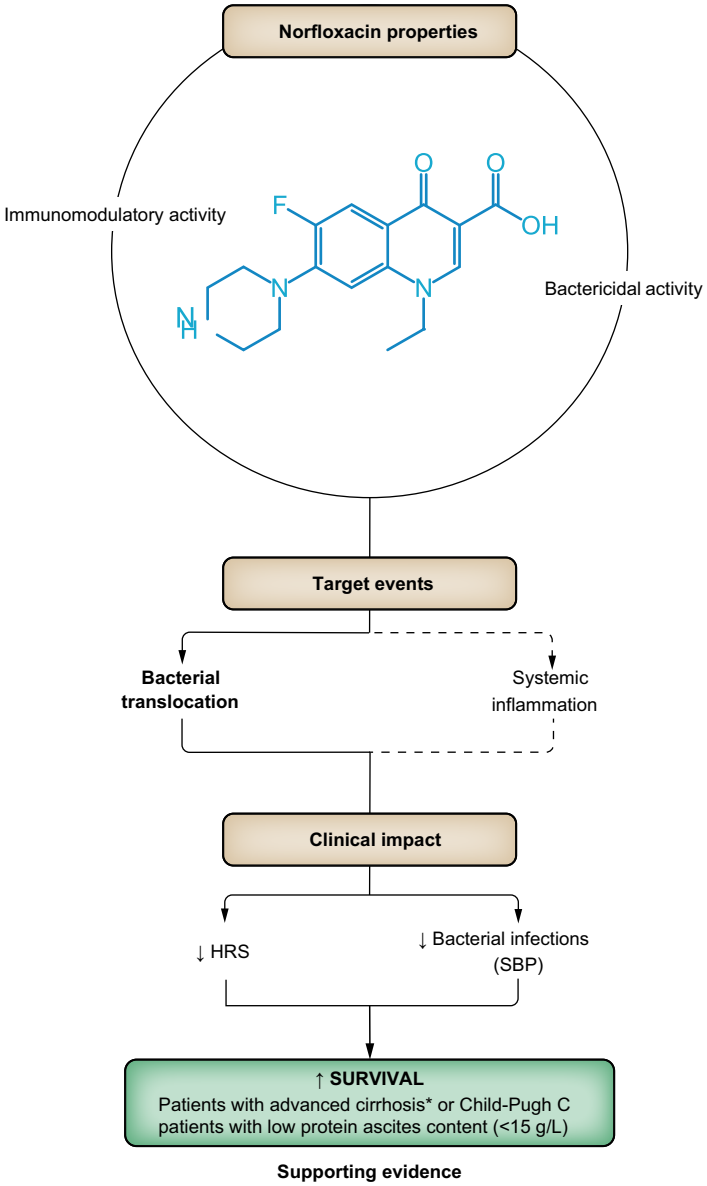

Fig. 2. Mechanisms of action, target events and clinical impact of norfloxacin as a candidate disease-modifying agent in decompensated cirrhosis. HRS, hepatorenal syndrome; RCT, randomised clinical trial; SBP, spontaneous bacterial peritonitis. *advanced cirrhosis is defined by severe liver failure (Child-Pugh ≥9 with serum bilirubin ≥3 mg/dl) or impaired renal function (serum creatinine ≥1.2 mg/dl, blood urea nitrogen ≥25 mg/dl or serum sodium ≤130 mEq/L) (reference 39).

Poorly absorbable antibiotics

Norfloxacin. Norfloxacin has been widely used since the 1990s in patients with decompensated cirrhosis for the selective intestinal decontamination of gram-negative bacteria to prevent bacterial translocation and thus the development of spontaneous bacterial peritonitis (SBP). In fact, norfloxacin reduces the circulating levels of markers of bacterial translocation and systemic inflammation and improves circulatory dysfunction[37] (Fig. 2). In addition, based on favourable trials and meta-analyses,[38–41] norfloxacin is currently recommended by international guidelines for the primary prophylaxis of SBP in patients with ascites at high-risk (Child-Pugh score ≥9 and serum bilirubin level ≥3 mg/dl, with either impaired renal function or hyponatremia, and ascitic fluid protein lower than 15 g/L) and for secondary prophylaxis against SBP recurrence.[42]

However, since norfloxacin acts effectively on bacterial translocation, which is a key initial event in the pathophysiological cascade of decompensated cirrhosis, its clinical benefit could be extended beyond the sole prevention of SBP. This hypothesis was recently tested by a large French multicentre, double-blind RCT in Child-Pugh C patients with ascites receiving norfloxacin (400 mg/day) or placebo for 6 months.[8] Unfortunately, no differences were observed between the 2 groups in terms of 6-month mortality, which was the primary outcome of the study. In contrast, *post hoc* analyses revealed that the cumulative incidence of death at 6 months was significantly reduced in the subgroup of patients with a low ascitic protein content (<15 g/L).

Norfloxacin does not thus appear to satisfy the major requirement of a disease-modifying agent even in the subgroup of Child-Pugh C patients with less than 15 g/L of protein in their ascites, since the benefit on survival was only demonstrated by a *post hoc* analysis. Furthermore, there are concerns about the safety of long-term administration because of the increased incidence of multi-drug resistant bacterial infections reported over 2 decades in patients receiving norfloxacin prophylaxis,[43] although this finding was not consistently confirmed in more recent studies.[8,44] In conclusion, the use of norfloxacin as a disease-modifying agent cannot currently be proposed.

Rifaximin. Rifaximin is a minimally absorbed oral antibiotic with activity against gram-negative and gram-positive bacteria which is unlikely to induce antibiotic resistance. Rifaximin appears to have beneficial effects on the gut-liver axis by improving gut epithelial layer homeostasis, decreasing inflammatory pathways, impairing bacterial attachment to enterocytes, and modulating the gut microbiome [45,46] (Fig. 3).

The only current indication for rifaximin in cirrhosis is the prevention of recurrent hepatic encephalopathy.[42] However, because of its activity against bacterial translocation and its good safety profile, the use of rifaximin as a disease-modifying agent represents an attractive option. In addition, several observational studies and a few small-scale RCTs [47–59] have associated rifaximin treatment with a better control of difficult-to-treat/refractory ascites,[47,48] the reduced incidence of decompensation, all-cause hospitalisations and readmissions, SBP, variceal bleeding, and acute kidney injury-hepatorenal syndrome (AKI-HRS) with a decreased risk of renal replacement therapy.[49–56] An improvement in mortality has also been suggested in some studies.[48,52] However, the overall low quality of the evidence available, as highlighted by several meta-analyses,[57–59] precludes the possibility of reaching any definite conclusion on the global impact of rifaximin on the course of decompensated cirrhosis.

We eagerly await the results of ongoing, large, multicentre, double-blind RCTs testing the impact of rifaximin, either alone or in combination with simvastatin, on survival or ACLF development (Table 1) in patients with decompensated cirrhosis.

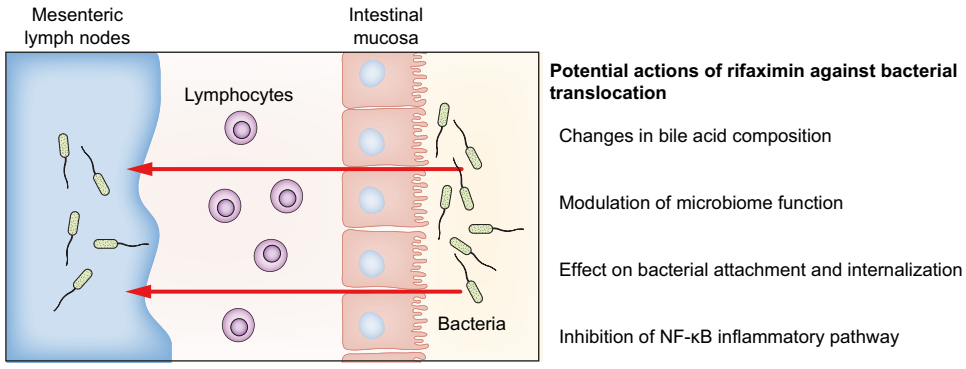

Fig. 3. Proposed potential mechanisms of action of rifaximin which could interfere with bacterial translocation in decompensated cirrhosis. See reference 45.

Table 1. Ongoing RCTs assessing currently available drugs as disease-modifying agents in patients with decompensated cirrhosis (from www.clinicaltrial.gov).

Title	Intervention	Design	Location	Primary outcome	NCT number
Statins for prevention of disease progression and hospitalisation in liver cirrhosis (*STATLiver*)	Atorvastatin 10-20 mg daily for up to 18 months	Randomised, double-blind, placebo-controlled	Denmark	Composite endpoint of numbers of death or liver transplantation	NCT04072601
Efficacy of the combination of simvastatin plus rifaximin in patients with decompensated cirrhosis to prevent ACLF development (*LIVERHOPE*)	Simvastatin 20 mg daily + rifaximin 400 mg every 8 hours for up to 12 months	Randomised, double-blind, placebo-controlled	Europe	Incidence of ACLF at 12 months. 1-, 3-, 6-, 9- and 12-month transplant-free survival as secondary outcome	NCT03780673
Albumin infusion effects in mortality in patients with cirrhosis and hepatic encephalopathy (*BETA*)	1.5 g/kg/day in the 24-48 hours after admission and 1 g/kg/day 72 hours after the first dose	Randomised, double-blind, placebo-controlled	Spain	Survival at 90 day	NCT02401490
Effects of long-term administration of human albumin in subjects with decompensated cirrhosis and ascites (*PRECIOSA*)	1.5 g/kg b.w. 20% albumin every 10 days for up to 12 months	Randomised, open-label, controlled	United States and Europe	1-year transplant-free survival	NCT03451292
Two strategies of primary prophylaxis of spontaneous bacterial peritonitis in severe cirrhotic patients with ascites (*ProPILARifax*)	Rifaximin 550 mg daily up to 12 months	Randomised, double-blind, placebo-controlled	France	12-month all-cause mortality	NCT03069131

ACLF, acute-on-chronic liver failure; RCT, randomised clinical trial.

These trials should confirm whether rifaximin can be repurposed and its indication extended beyond preventing the recurrence of hepatic encephalopathy.

Statins

Statins are a heterogeneous group of molecules which have been used for decades to manage hypercholesterolemia because of their ability to inhibit the activity of the hydroxymethylglutaryl-coenzyme A reductase, a key enzyme in the synthesis of cholesterol. Statins also exhibit antioxidative, antiproliferative and anti-inflammatory properties, improve endothelial function, and promote neoangiogenesis.[60,61]

Statins were initially proposed for the treatment of portal hypertension in the early 2000s. The rationale was that statins could restore the decreased nitric oxide production in the liver sinusoid and thus decrease intrahepatic resistance and portal pressure.[62] Subsequent studies in experimental models of cirrhosis showed that statins have additional systemic and liver anti-inflammatory activities and hepatoprotective effects.[63–67] The molecular mechanisms mediating the hepatic effects of statins include the upregulation of endothelial Kruppel-like factor 2 (KLF2),[65] a transcription factor that regulates the expression of a wide variety of vasoprotective genes involved in the control of apoptosis, inflammation, oxidative stress, thrombosis and vasodilation, as well as the inhibition of RhoA/Rho-kinase signalling, which is partly responsible for the contractility of hepatic stellate cells[66] (Fig. 4).

Based on the results of proof-of-concept and phase II RCTs showing that statins decrease portal pressure in patients with cirrhosis,[67–69] a large double-blind multicentre RCT was conducted comparing simvastatin (40 mg/day) with a placebo added to standard therapy (endoscopic variceal ligation and NSSBs). The aim was to assess whether this could decrease rebleeding and death after an episode of variceal bleeding in patients with cirrhosis.[70] Simvastatin failed to show a benefit on the primary endpoint, which was a composite of rebleeding and death. However, while no effect was observed on the incidence of rebleeding, a significant reduction in mortality occurred in the group of patients treated with simvastatin. *Post hoc* analyses confirmed the survival benefit in patients with Child-Pugh A/B cirrhosis, but not in those with Child-Pugh C cirrhosis. This apparent contradiction (not preventing rebleeding but improving survival) suggests that the effect on portal pressure might be less relevant than the other pleiotropic activities of statins that attenuate the inflammatory response, which characterises advanced cirrhosis[60,61] and plays a major role in the development of ACLF and mortality.[13,14,72]

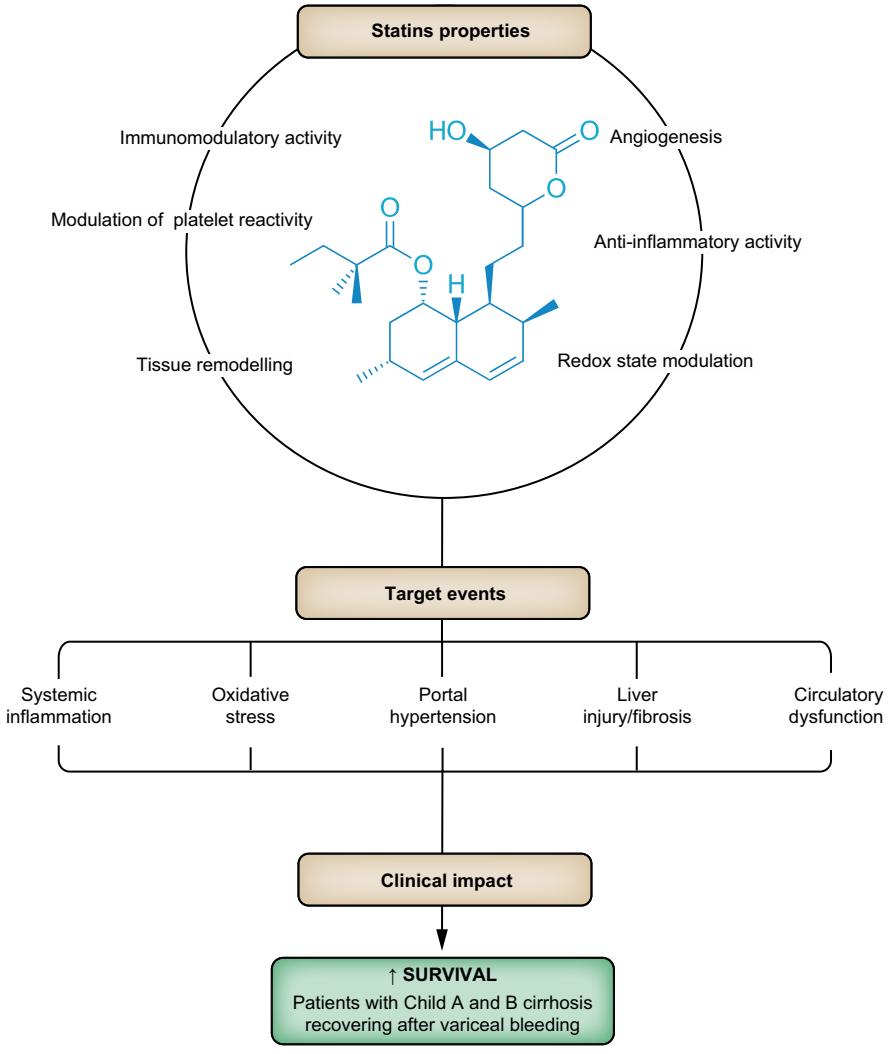

Fig. 4. Mechanisms of action, target events and clinical impact of statins as a candidate disease-modifying agent in decompensated cirrhosis. RCT, randomised clinical trial.

From being relatively contraindicated because of the concern that statins cause hepatotoxicity,[73] the aforementioned evidence has thus prompted researchers to further assess their efficacy in slowing down disease progression in patients with decompensated cirrhosis. An example is the ongoing LiverHope Efficacy trial, a double-blind, multicentre RCT, comparing simvastatin (20 mg/day) plus rifaximin (1,200 mg/day) with placebo for 12 months in patients with Child-Pugh B and C cirrhosis (www.liverhope-h2020.eu). Similarly, the STATliver trial, a double-blind, multicentre RCT, is comparing atorvastatin (20 mg/day) with placebo for 18 months in patients with clinically significant portal hypertension, an MELD score of up to 23, and a Child-Pugh score of up to 13 (Table 1).

Besides efficacy, these ongoing trials should also clarify whether the use of statins in patients with very advanced liver disease is associated with any safety issues, as the pharmacokinetics of statins are markedly altered in patients with decompensated cirrhosis. In fact, the incidence of muscle toxicity with simvastatin at a daily dose of 40 mg could be up to 30x higher in these patients than in the general population.[70] Recent data from the LiverHope Safety trial, a double-blind, placebo-controlled dose-finding study conducted in patients with Child-Pugh B and C cirrhosis, showed that a dose of 20 mg/day was associated with no

significant muscle toxicity, while 40 mg/day induced a marked elevation of creatinine kinase and transaminases with severe rhabdomyolysis observed in 3 out of 16 patients.[74]

In conclusion, the results of the ongoing RCTs, which will define the efficacy and safety of statins, as well as their potential target population in patients with decompensated cirrhosis, are eagerly awaited.

Human albumin

Based on its oncotic and non-oncotic properties, besides promoting plasma volume expansion to improve effective hypovolemia, human albumin has been shown to simultaneously act on several other pathophysiological mechanisms of decompensated cirrhosis by binding endogenous and exogenous compounds, exerting antioxidant activity, modulating inflammation and immune

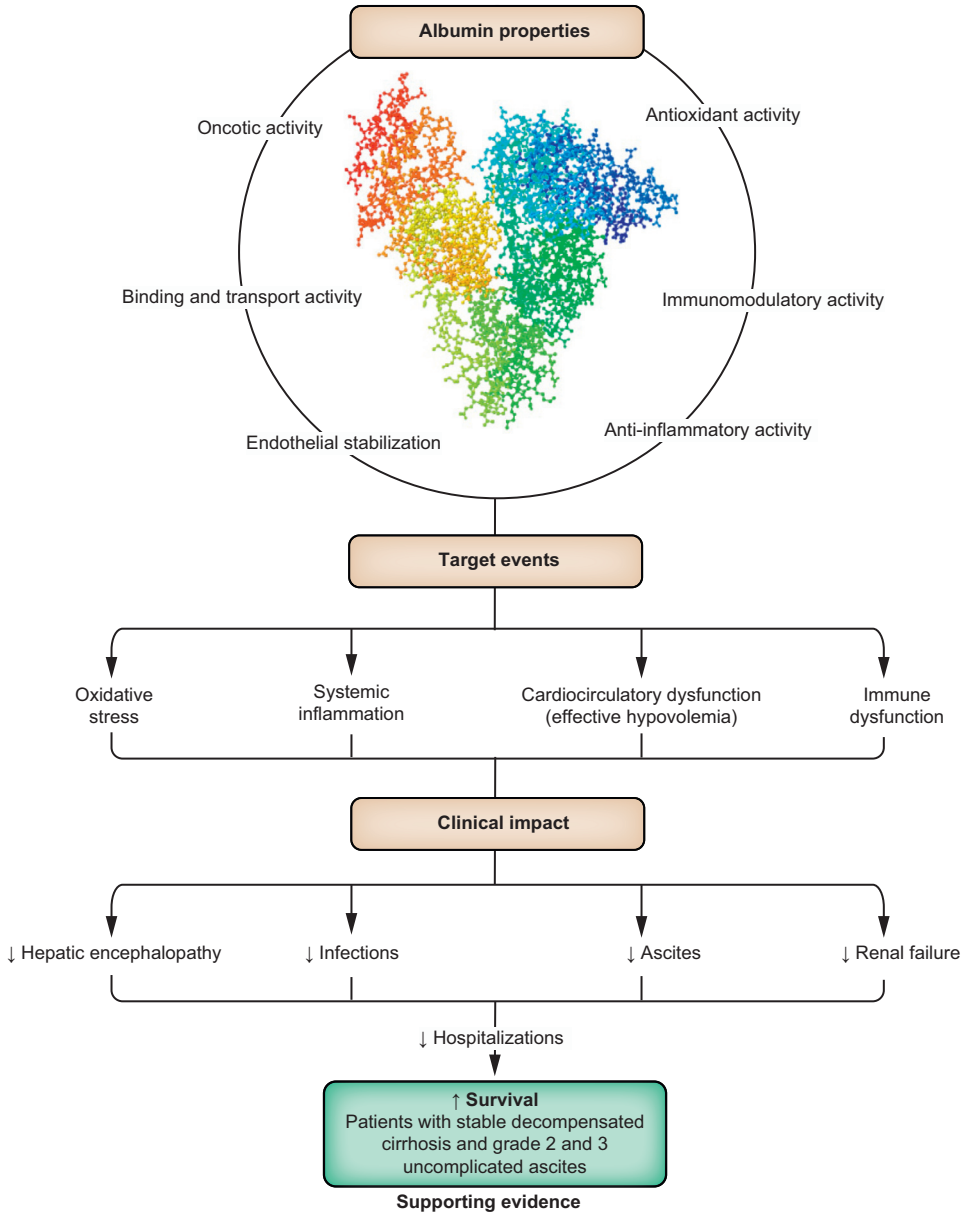

Fig. 5. Mechanisms of action, target events and clinical impact of human albumin as a candidate disease-modifying agent in decompensated cirrhosis. RCT, randomised clinical trial.

responses, improving cardiac function, and restoring endothelial integrity.[75,76] From a pathophysiological perspective, human albumin administration could therefore be proposed as a multi-target agent in decompensated cirrhosis (Fig. 5). Acute or short-term human albumin administration is currently recommended by international guidelines to prevent post-paracentesis circulatory dysfunction, to improve survival after SBP, and to treat HRS in association with vasoconstrictors.[42,77]

Since 2018, 3 large RCTs have been completed, thus opening up the possibility of extending the current indications for human albumin in patients with decompensated cirrhosis.[5–7] In the ANSWER study,[5] an open-label, multicentre RCT, which enrolled patients with stable decompensated cirrhosis and uncomplicated grade 2 and 3 ascites, significantly better 18-month overall survival (primary endpoint) was demonstrated in those receiving human albumin, with a 38% reduction in the mortality hazard ratio. Human albumin clearly eased the management of ascites and significantly lowered the incidence rate of severe complications. As a result, the number and length of liver-related hospitalisations were significantly reduced and the progressive worsening of the quality of life seen in patients only receiving standard medical treatment was significantly attenuated in those receiving human albumin. In contrast, the MACHT study,[6] a multicentre, double-blind RCT in patients with ascites listed for liver transplantation, showed no differences in either the probability of developing complications (primary endpoint) or death between patients receiving human albumin or not for up to 12 months. Finally, in the ATTIRE study,[7] an open-label, multicentre RCT, which included patients admitted to hospital for acute decompensation of cirrhosis with or without ACLF, albumin treatment for up to 14 days was not associated with any improvement in the incidence of all-cause infection, renal dysfunction, and death (composite primary endpoint).

These divergent results clearly indicate that human albumin can be effective in certain patients with decompensated cirrhosis but not in others. The 3 studies differed in terms of design, baseline patient characteristics, length of follow-up, and dosage and timing of albumin administration (Table 2). Their comparison provides very useful insights into the repurposing of human albumin. First, human albumin does not appear to modify the course of cirrhosis in very sick patients admitted to hospital for an acute complication, at least with the dose and schedule of administration chosen in the ATTIRE study.[7] This is consistent with the negative results emerging from other RCTs published on the use of human albumin for short-term treatment (up to 2 weeks) of acute complications of cirrhosis, such as non-SBP bacterial infections or acute episodes of overt hepatic

Table 2. Comparison of the main features of the ANSWER, MACTH and ATTIRE trials.

	ANSWER	MACHT	ATTIRE
Study population	Patients with uncomplicated grade 2 and 3 ascites	Patients with ascites listed for liver transplantation	Patients hospitalised for acute decompensation of cirrhosis
Trial design	Multicentre open-label randomised clinical trial	Multicentre double-blind randomised clinical trial	Multicentre open-label randomised clinical trial
Intervention	40 g of albumin twice a week for 2 weeks, then 40 g weekly	40 g every 2 weeks plus midodrine adjusted to changes in mean arterial pressure	Targeted to maintain a serum albumin level >3.0 g/dl from day 3
Primary endpoint	Overall survival	Incidence of complications of cirrhosis	Composite of incidence of all-cause infection, renal dysfunction and death
Planned maximal length of treatment	18 months	12 months	14 days
ITT population (intervention/control)	431 (218/213)	173 (87/86)	777 (380/397)
Baseline MELD score (intervention/control)	Median (IQR) 12 (10-15)/13 (10-16)	Mean ± SD 17 ± 6/16 ± 6	Median (IQR) 19.6 (15.4-22.9) / 19.5 (15.4-23.4)
Median follow-up (intervention/control)	17.6/11.5 months	63/105 days	——
Effect on serum albumin concentration	Significant and stable increase in the albumin arm	No difference between the 2 arms	Significant increase in the albumin arm
Impact on complications of cirrhosis	Reduced incidence of complications of cirrhosis in the albumin arm	No difference between the 2 arms	No difference between the 2 arms
Impact on survival	Increased survival in the albumin arm	No difference between the 2 arms	No difference between the 2 arms

ITT, intention-to-treat; MELD, model for end-stage liver disease.

encephalopathy.[78–81] To date, short-term human albumin administration has been clearly demonstrated to be effective only in patients suffering SBP or HRS (if associated with vasoconstrictors).[42] Second, a clear definition of the target subgroup and the modalities of administration are also needed in the case of long-term albumin treatment. Among the several differences between the ANSWER and MACHT studies, including the different median length of follow-up, which was only 2 months in the MACHT trial due to the high transplantation rate in Spain, a major variant was the fact that the dose of albumin in the MACHT trial was half that in the ANSWER trial and no loading dose was given. A major consequence was the different impact on serum albumin concentration, which remained close to the baseline level of 3.1 g/dl in the MACHT trial [6] but increased by 0.6–0.8 g/L to almost 4 g/dl in the ANSWER study.[5] A subsequent *post hoc* analysis of the latter trial showed that the serum albumin concentration reached after 1 month of treatment predicted the probability of 18-month overall survival, which was greater than 90% in patients with serum albumin ≥4 g/dl.[82] The importance of increasing the serum albumin concentration beyond a certain level is further supported by 2 other pieces of evidence. In the pilot-PRECIOSA study, an improvement in circulatory dysfunction and systemic inflammation was achieved only in the group of patients receiving human albumin at the higher dose (1.5 g/kg b.w. every week), which increased serum albumin concentration close to 4 g/dl, but not in those receiving the lower dose (1 g/kg b.w. every 10 days), which did not normalise serum albumin levels.[83] Furthermore, more than 90% of healthy adult individuals present a serum albumin concentration greater than 4 g/dl.[84]

Taken together, the above evidence indicates that long-term human albumin administration can satisfy many of the requirements of a disease-modifying agent listed in Box 1, at least in the subgroup of patients presenting with stable decompensated cirrhosis and grade 2 or 3 uncomplicated ascites.

However, an important limitation of the ANSWER study relates to its open-label design, with more frequent access to healthcare services in the treatment group owing to their need for weekly albumin infusions. This could represent a confounding factor in the interpretation of the results, although the pragmatic nature of the study, large sample size and strong endpoints may have mitigated this bias. Data from the ongoing multicentre PRECIOSA trial (Table 1) assessing long-term human albumin administration (1.5 g/kg/b.w. every 10 days) for 12 months in patients with ascites are thus required to confirm the role of human albumin as a disease-modifying agent and to extend its indication to a wider group of patients with decompensated cirrhosis.

Other interventions

Transjugular intrahepatic portosystemic shunt. Portal hypertension plays a causal role in most cirrhosis complications. Therefore, a transjugular intrahepatic portosystemic shunt (TIPS), which normalises the portal pressure gradient,[85] can potentially modify the natural history of the disease. The timing of TIPS and the identification of target patients are the contentious points when considering TIPS as a disease-modifying agent.

To date, the capacity of TIPS to modify the course of cirrhosis has been demonstrated by 3 RCTs when given 'pre-emptively'. In patients at high risk of uncontrolled bleeding and bleeding-related mortality (HVPG >20 mmHg, Child-Pugh C [10-13 points], or B with active bleeding), TIPS insertion within 24 or 72 hours controls bleeding/prevents rebleeding and improves survival[86–88] (Box 1). Interestingly, 2 recent large observational studies suggest that TIPS improves survival in patients with acute variceal bleeding and ACLF.[89,90]

The results of TIPS placed in patients with ascites are more controversial. Seven RCTs have compared TIPS and large-volume paracentesis plus albumin, the standard therapy for patients with refractory ascites.[91–97] Although TIPS was more effective in controlling ascites in all trials, a significant advantage in transplant-free survival was demonstrated when TIPS was performed with covered stents [97] or in the studies including patients with 'recurrent' or 'recidivant' ascites who did not fully meet the stringent criteria of refractory ascites [92,95,97] or presented a less severe disease.[96] A strong limitation of the use of TIPS in these patients is the high incidence of adverse events, the most frequent being hepatic encephalopathy, cardiac dysfunction, and liver failure.[85] TIPS cannot therefore be used in most potential candidates, thus greatly limiting TIPS as a disease-modifying agent in patients with ascites.

Non-selective beta-blockers. Based on their capacity to decrease portal pressure, NSBBs are currently recommended for the primary and secondary prophylaxis of portal-hypertensive gastrointestinal bleeding.[42,98,99] NSBBs also seem to have non-haemodynamic effects, including decreasing intestinal permeability, bacterial translocation and systemic inflammation.[100]

The efficacy and safety of NSBBs in patients with decompensated cirrhosis has been one the most controversial issues among hepatologists in the last decade,[101] and a detailed analysis is beyond the scope of the present review. At present, there are insufficient data to prescribe NSBBs in patients with decompensated cirrhosis beyond the current indication of bleeding prophylaxis, as the evidence

in favour of the use of NSBBs is still limited to a single RCT showing fewer infections and less kidney dysfunction in patients with ACLF.[102] Nonetheless, the repurposing of NSBBs for decompensated cirrhosis beyond the prevention of bleeding represents an important topic for future research.

Granulocyte colony-stimulating factor. The effects of granulocyte colony-stimulating factor (G-CSF), either alone or in combination with bone-marrow stem cell transplantation, on the outcome of patients with acute alcoholic hepatitis and/or ACLF [103–110] or patients with stable decompensated cirrhosis[111–115] have been assessed in small RCTs. Drawing definitive conclusions is challenging because of the high level of heterogeneity between studies and the different outcomes reported in Europe and Asia.[116] At present, there is insufficient evidence to support the repositioning of G-CSF in patients with decompensated cirrhosis beyond its established indication for treating neutropenia.

Extracorporeal assist devices and treatments. Several artificial and bioartificial extracorporeal liver support systems (coupled or not with systems for the support of other organs) have been developed in the last 2–3 decades, with the aim of improving transplant-free survival or as a bridge to transplantation in patients with acute liver failure or ACLF.[117,118] However, RCTs have so far not unequivocally proven their efficacy in improving survival.[119–121] The improved understanding of the pathobiology of advanced cirrhosis has recently fostered the development of new systems and methodologies, which are currently under clinical evaluation. The ALIVER consortium, very recently reported promising preliminary results in terms of the safety and tolerability of Dialive™ in patients with ACLF. Dialive is a new dual filtration system that includes 2 specialised filters for removing toxic products from blood and replacing damaged albumin with fresh albumin (www.aliver.info). Another approach based on the non-oncotic properties of albumin[76,77] is currently under investigation in the APACHE trial, a large multicentre RCT comparing the effect on 90-day overall survival of total plasma exchange with 5% albumin on top of standard medical treatment *vs.* standard medical treatment alone in patients with ACLF (primary endpoint) (ClinicalTrial identifier: NCT03702920).

Drug repurposing in decompensated cirrhosis: future perspectives

The drug repurposing described stems from the work of researchers, who have formulated new hypotheses (based on increasing knowledge of drug activities and pathogenesis of decompensated cirrhosis) and then tested these hypotheses in experimental and clinical studies.

However, in the last decade, the development of high-throughput technologies and the advent of big data repositories and associated analytical methods, in addition to the increasing interest of scientists, institutions and pharmaceutical companies, have led to the development of systematic approaches to drug repurposing.[15,122] An example of such an approach in relation to decompensated cirrhosis is the DECISION project. A series of -omics technologies (genomics, transcriptomics, proteomics, metabolomics) are being applied to 3 large international cohorts consisting of more than 2,500 patients admitted to hospital for acute decompensation of cirrhosis, with or without ACLF, with detailed clinical data, treatment history and outcomes, and biological samples (www.decision-for-liver.eu). Using a systems medicine approach, the aim of the DECISION consortium is to identify a combinatorial treatment, made up of 2–3 drugs among those already on the market, to be tested in a proof-of-concept trial in hospitalised patients with cirrhosis at high risk of developing ACLF.

New drug discovery

The improved understanding of the molecular mechanisms underlying decompensated cirrhosis has also prompted a search for new interventions, drugs and biological substances, which are capable of acting on key steps in the pathogenetic network, *e.g.* the gut-liver axis, systemic inflammation, and immune dysfunction. As the entire process of drug discovery is much longer and more expensive than drug repurposing, because of the requirement to go through all the pre-clinical and clinical phases before obtaining regulatory approval,[15] new candidate interventions for decompensated cirrhosis are still under evaluation in pre-clinical experimental models or, in very few cases, in early clinical trials.

The gut-liver axis is an attractive target as it is an initiating event, located upstream in the pathophysiological cascade of decompensated cirrhosis.[123]

Among several non-antibiotic interventions under pre-clinical development, Carbalive™, a novel engineered macroporous carbon bead with a particular physical structure, has completed the first clinical step. Carbalive is orally administered and designed to adsorb and remove lipopolysaccharide (LPS) and other toxins from the gut, thus preventing their translocation into the blood and liver where they can trigger a cascade of responses leading to inflammation and immune dysfunction. The CARBALIVE consortium, has very recently reported (www.carbalive.eu) positive preliminary results of a controlled, double-blinded RCT investigating the safety and tolerability of Carbalive, compared to placebo, over a 3-month treatment period in patients with stable decompensated cirrhosis, thus supporting its further evaluation in efficacy RCTs.

Key point

Repurposing drugs that have already been prescribed with more limited or non-hepatic indications has recently provided a few candidate disease-modifying agents (*i.e.* poorly-absorbable oral antibiotics, statins, human albumin) in decompensated cirrhosis, which are currently under further evaluation in large-scale randomised clinical trials.

Key point

New disease-modifying agents are also expected to be identified in the next decade through the systematic repurposing of existing drugs and the development of novel molecules acting on key pathophysiological mechanisms.

Given the central role of inflammation and immune dysfunction in the pathogenesis of decompensated cirrhosis and particularly ACLF,[13,14,71] targeting mechanisms underlying inflammatory and immune responses is a key topic, although it is expected that many interventions identified in pre-clinical testing will fail to confirm their efficacy when tested in RCTs due to the great redundancy in pathogenetic networks.

Toll-like receptor 4 (TLR4) is a pattern recognition receptor which primarily binds circulating pathogen-associated molecular patterns (LPS and gram-negative endotoxins), and damage-associated molecular patterns (cleaved nucleosomes, histones, high-mobility group box 1 proteins [HMGB1]).[124,125] Binding triggers the recruitment of adaptor molecules, including the TIR domain-containing adaptor protein (TIRAP)-MyD88, which results in the activation of NF-kB, and the TRIF-related adaptor molecule (TRAM)-TRIF, which induces cytokine and interferon production, thus eliciting the inflammatory response.[126] TAK-242, a specific inhibitor of the TLR4 receptor, selectively disrupts TLR4 signalling by directly binding to the intracellular TIR domain, resulting in impaired recruitment of both TIRAP and TRAM.[126] TAK-242 appears to reduce the severity of inflammation and hepatocyte cell death and to improve organ function in experimental models of ACLF and acute liver failure.[127] Based on the positive pre-clinical results, a double-blind, placebo-controlled, multicentre RCT has been planned, with the aim of assessing the efficacy, safety, pharmacokinetics, and pharmacodynamics of intravenous TAK-242 in patients with acute alcoholic hepatitis causing decompensation of alcohol-related cirrhosis and ACLF (ClinicalTrial.gov identifier: NCT04620148). Inhibition of the TLR4/LPS pathway is also the target of other candidate molecules, such as the recombinant alkaline phosphatase (recAP), which was developed from the finding that alkaline phosphatase is not only a biomarker of cholestasis, but also has anti-inflammatory activity as it detoxifies free nucleotides and bacterial LPS.[128] The administration of recAP has been shown to improve experimental ACLF by reducing the activation of TLR4.[129]

Oxysterol sulfates are a new class of anti-inflammatory drugs under early clinical evaluation. They decrease lipid biosynthesis, suppress inflammatory responses, and promote cell survival by acting through epigenetic modification.[130,131] The intravenous administration of one of these oxysterol sulfates, DUR-928, has been evaluated in a pivotal, phase IIA, open-label study enrolling 19 patients with moderate-severe acute alcoholic hepatitis. Based on promising safety and efficacy signals,[132,133] phase IIB studies have now been planned (ClinicalTrials.gov identifiers: NCT03917407 and NCT04563026).

It is also probable that among the many molecules with anti-inflammatory properties that are currently under evaluation in non-alcoholic steatohepatitis or in other non-hepatic diseases,[134] some will have an acceptable safety profile and could also be tested in the relatively near future in patients with decompensated cirrhosis and ACLF.

Conclusions

Apart from aetiological treatments, disease-modifying agents that can antagonise key pathophysiological mechanisms of decompensated cirrhosis remain an unmet need. However, repurposing "old drugs" that are already prescribed for more limited indications in hepatology or for other diseases has provided a shortlist of candidates (with human albumin the most advanced), which are being evaluated in large-scale RCTs. New disease-modifying agents are expected to be identified in the next few years by systematic drug repurposing and the development of novel molecules currently undergoing pre-clinical or early clinical testing. Hopefully, a decade from now, guidelines will recommend the use of disease-modifying agents capable of slowing down the course of the disease in many patients with decompensated cirrhosis.

Abbreviations

ACLF, acute-on-chronic liver failure; G-CSF, granulocyte colony-stimulating factor; HRS, hepatorenal syndrome; LPS, lipopolysaccharide; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NSBBs, non-selective beta-blockers; RCT, randomised clinical trials; recAP, recombinant alkaline phosphatase; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt; TIRAP, TIR domain-containing adaptor protein; TLR4, Toll-like receptor 4; TRAM, TRIF-related adaptor molecule.

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Conflict of interest

Dr. Caraceni reports personal fees from Grifols SA, grants and personal fees from Octapharma SA, personal fees from Kedrion Biopharma SpA, personal fees from Mallinkrodt SA, personal fees from Gilead SA, personal fees from Takeda Sa, outside the submitted work. Dr. Ginès reports grants and personal fees from Grifols, grants and personal fees from Gilead, grants and personal fees from Mallinckrodt, personal fees from Martin pharmaceuticals, personal fees from Novartis, personal fees from Intercept, from null, outside the submitted work. Dr. Abraldes, Dr. Newsome and Dr. Sarin have nothing to disclose.

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