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Namodenoson Treatment in Decompensated Cirrhosis: Clinical–Hemodynamic Improvement Enabling Bridging to Liver Transplantation

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Abbreviations:

A3AR: A3 Adenosine Receptor; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AMA: Anti-Mitochondrial Antibodies; ANA: Anti-Nuclear Antibodies; ASMA: Anti-Smooth Muscle Antibodies; AST: Aspartate Aminotransferase; CF102: Namodenoson; EGD: Esophagogastroduodenoscopy; GGT: Gamma-Glutamyl Transferase; IgG: Immunoglobulin G; IgM: Immunoglobulin M; INR: International Normalized Ratio; MELD: Model for End-Stage Liver Disease; NF-κB: Nuclear Factor Kappa B; PBC: Primary Biliary Cholangitis; UDCA: Ursodeoxycholic Acid

1. Abstract

Decompensated cirrhosis is associated with high morbidity and mortality, and liver transplantation remains the only definitive treatment. Strategies that enable clinical stabilization and safe bridging to transplantation represent a critical unmet need.

Namodenoson, a selective A3 adenosine receptor (A3AR) agonist, has shown anti-inflammatory and anti-fibrotic effects in preclinical models, potentially through modulation of NF-κB and Wnt/β-catenin signalling pathways.

We describe a patient with advanced cirrhosis secondary to primary biliary cholangitis and steatotic liver disease who developed hepatic decompensation and was listed for liver transplantation. Treatment with namodenoson under a compassionate use protocol was associated with resolution of ascites, regression of esophageal varices, and reduction in globulin levels, suggesting improvement in portal hypertension and systemic immune activation. Notably, these clinical improvements occurred despite continued deterioration in hepatic synthetic function.

The patient remained clinically stable for 28 months and was successfully bridged to orthotopic liver transplantation.

This observation provides a hypothesis-generating clinical signal supporting A3AR agonism as a potential disease-modifying strategy in decompensated cirrhosis, particularly as a bridge-to-transplant approach.

2. Introduction

Liver cirrhosis represents the end stage of chronic liver disease and is characterized by progressive fibrosis, portal hypertension, and impaired hepatic function [1]. Once decompensation occurs, manifested by ascites, variceal bleeding, or hepatic encephalopathy, prognosis significantly worsens, and liver transplantation remains the only curative option [2,3]. However, limited donor-organ availability creates a critical need for therapies that can stabilize patients safely while they await transplantation.

Despite advances in understanding the pathophysiology of cirrhosis, pharmacological interventions capable of modifying its progression remain limited. Chronic inflammation, immune dysregulation, increased intrahepatic vascular resistance, and activation of pro-fibrotic pathways contribute to portal hypertension and clinical decompensation [4].

The A3 adenosine receptor (A3AR) is a Gi protein-coupled receptor that is highly expressed in inflammatory and pathological cells. A3AR activation has been reported to produce anti-inflammatory and anti-fibrotic effects, in part through inhibition of NF-κB signalling and modulation of downstream inflammatory mediators [5].

Namodenoson (CF102), a selective A3AR agonist, has demonstrated hepatoprotective and anti-inflammatory activity in preclinical studies and clinical activity in liver diseases, including metabolic dysfunction-associated steatohepatitis and hepatocellular carcinoma in patients with underlying cirrhosis [6–8].

Here, we describe a patient with advanced decompensated cirrhosis who received namodenoson under compassionate use. The obser vation is notable for improvement in portal hypertension-related

complications despite continued deterioration in hepatic synthetic function, enabling successful bridging to liver transplantation.

3. Case Report

A 53-year-old female from southern Israel was referred in 2016 to the Soroka University Medical Center (SUMC) liver clinic due to persistent elevation of liver enzymes and fatigue. Her past medical history was notable for morbid obesity and dermatitis herpetiformis, without chronic medical therapy.

Review of her medical records revealed a longstanding cholestatic pattern of liver enzyme abnormalities over the preceding decade. Alkaline phosphatase (ALP) levels ranged between 500–600 U/L, and gamma-glutamyl transferase (GGT) levels were similarly elevated (400–500 U/L). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were consistently 2–3 times the upper limit of normal. Platelet counts declined progressively from >200 $\times 10^3/\mu L$ in 2005 to 81 $\times 10^3/\mu L$ at presentation. Notably, bilirubin levels remained within normal limits at that time. Liver synthetic function was preserved, with an international normalized ratio (INR) of 1.0 and serum albumin of 4.2 g/dL.

Immunological evaluation demonstrated elevated globulin levels (5 g/dL), with a predominance of immunoglobulin G (IgG, 3081 mg/dL) and immunoglobulin M (IgM, 539 mg/dL). Viral hepatitis serologies were negative. Autoimmune workup revealed positive anti-mitochondrial antibodies (AMA), while anti-nuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) were negative.

Abdominal ultrasound demonstrated a nodular liver with evidence of steatosis. Portal hypertension was evident, with splenomegaly measuring 17 cm and an enlarged portal vein (1.5 cm diameter). Esophagogastroduodenoscopy (EGD) revealed small esophageal varices and portal hypertensive gastropathy.

The patient was diagnosed with cirrhosis secondary to primary biliary cholangitis (PBC) with concomitant steatotic liver disease. Treatment with ursodeoxycholic acid (UDCA) at 15 mg/kg/day resulted in partial biochemical improvement, with ALP and GGT decreasing to <200 U/L, although not normalizing. Propranolol was initiated for portal hypertension.

In October 2019, the patient presented with severe hematemesis. Emergency EGD revealed large esophageal varices with red wale signs, and endoscopic band ligation was performed. Despite adherence to therapy, disease progression continued. By 2022, imaging demonstrated worsening portal hypertension, including splenomegaly (20 cm), portal vein dilation (2.5 cm), and extensive portosystemic collaterals. The patient subsequently developed ascites, requiring treatment with spironolactone and furosemide.

By July 2023, the patient exhibited clear signs of hepatic decompensation, including hyperbilirubinemia (3.0 mg/dL), hypoalbuminemia (2.8 g/dL), and coagulopathy (INR 1.5). The MELD 3.0 score was calculated at 18, and the patient was listed for liver transplantation.

In August 2023, the patient was enrolled in a compassionate use protocol at SUMC and initiated treatment with namodenoson (25 mg twice daily). Treatment was well tolerated with no reported drug-related adverse events. The patient reported subjective improvement in fatigue and overall well-being shortly after treatment initiation.

While cholestatic liver enzymes remained largely unchanged, a significant reduction in total globulin levels was observed (to 3.6 g/dL).

Importantly, imaging performed in August 2024 demonstrated complete resolution of ascites, allowing discontinuation of diuretic therapy. Follow-up EGD in August 2025 revealed only minimal residual esophageal varices, indicating improvement in portal hypertension.

Despite these clinical improvements, bilirubin levels continued to rise, reaching 7.7 mg/dL by December 2025. In January 2026, after approximately 28 months of continuous namodenoson therapy, the patient successfully underwent orthotopic liver transplantation from a deceased donor. Post-transplant recovery was favourable, with the patient in good clinical condition.

Serial FibroScan assessments were performed at treatment months 0, 6, 12, 18, 24, and 28 (Figure 1 and Table 1). Liver stiffness values were 35, 30, 28, 32, 36, and 40 kPa, respectively, demonstrating an initial decline followed by a gradual increase. All measurements remained within the cirrhotic range. The patient underwent orthotopic liver transplantation in January 2026 after approximately 28 months of treatment.

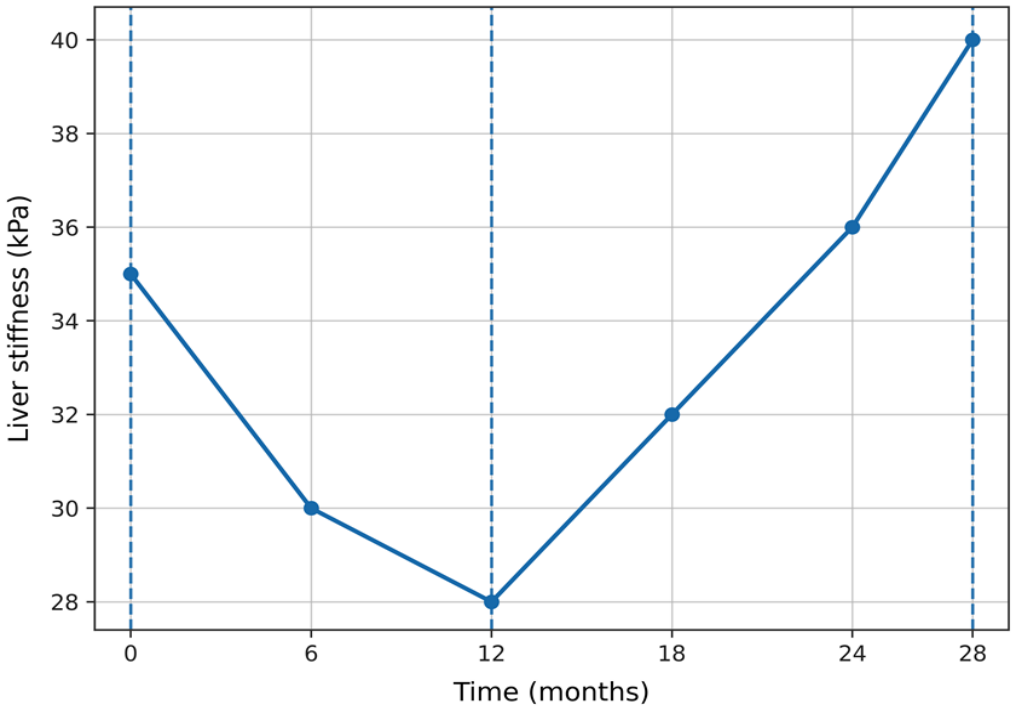

Figure 1: Longitudinal FibroScan liver stiffness measurements during namodenoson treatment. Time 0 corresponds to treatment initiation in August 2023; subsequent measurements were obtained at treatment months 6, 12, 18, 24, and 28. Values were 35, 30, 28, 32, 36, and 40 kPa, respectively. Liver stiffness remained within the cirrhotic range despite improvement in portal hypertension-related complications, illustrating a potential dissociation between structural liver disease and clinical/hemodynamic manifestations. Dashed vertical lines indicate initiation of namodenoson treatment (month 0), resolution of ascites with discontinuation of diuretics (month 12), and liver transplantation (month 28).

Table 1: Chronology of major clinical events, investigations, and treatment changes

Timing	Investigation/event	Key finding	Treatment/change
2016	Initial liver-clinic evaluation	Cirrhosis attributed to PBC with concomitant steatotic liver disease; small esophageal varices and portal hypertensive gastropathy	UDCA and propranolol initiated
October 2019	Severe hematemesis; emergency EGD	Large esophageal varices with red wale signs	Endoscopic band ligation
2022	Imaging and clinical follow-up	Worsening portal hypertension; splenomegaly (20 cm), portal vein 2.5 cm, extensive collaterals; ascites developed	Spironolactone and furosemide initiated
July 2023	Transplant assessment	Bilirubin 3.0 mg/dL, albumin 2.8 g/dL, INR 1.5; MELD 3.0 score 18	Listed for liver transplantation
August 2023 (month 0)	Compassionate-use treatment; FibroScan	Liver stiffness 35 kPa	Namodenoson 25 mg twice daily initiated
~February 2024 (month 6)	FibroScan	Liver stiffness 30 kPa	Namodenoson continued
August 2024 (month 12)	Imaging; FibroScan	Ascites resolved; liver stiffness 28 kPa	Diuretics discontinued; namodenoson continued
~February 2025 (month 18)	FibroScan	Liver stiffness 32 kPa	Namodenoson continued
August 2025 (month 24)	EGD; FibroScan	Minimal residual esophageal varices; liver stiffness 36 kPa	Namodenoson continued
December 2025	Laboratory follow-up	Bilirubin increased to 7.7 mg/dL	Awaiting transplantation
January 2026 (month 28)	FibroScan; transplantation	Liver stiffness 40 kPa	Orthotopic liver transplantation; namodenoson discontinued

4. Discussion

This clinical observation raises the hypothesis that A3AR agonism may have a supportive role in advanced cirrhosis, particularly as a bridge to transplantation. During namodenoson treatment, ascites resolved, diuretics were discontinued, esophageal varices regressed, and no further variceal bleeding occurred. These changes are clinically consistent with improvement in complications associated with portal hypertension. However, because hepatic venous pressure gradient was not measured, a direct reduction in portal pressure cannot be established.

The observed improvement may reflect effects on inflammatory and hemodynamic components of cirrhosis. Intrahepatic inflammation, endothelial dysfunction, increased sinusoidal resistance, and altered vascular tone contribute to portal hypertension [4,9]. A3AR activation inhibits NF-κB signalling and modulates pro-inflammatory cytokine production [5]. Namodenoson has also shown clinical activity and a favourable safety profile in patients with metabolic dysfunction-associated steatohepatitis and in patients with advanced hepatocellular carcinoma and Child–Pugh B cirrhosis [6–8]. These findings provide biological plausibility for the clinical pattern observed in this patient.

The marked reduction in serum globulin levels may additionally indicate attenuation of systemic immune activation. Cirrhosis is associated with intestinal dysbiosis, increased gut permeability, microbial translocation, and impaired hepatic reticuloendothelial clearance, processes that promote chronic immune stimulation and hypergammaglobulinemia [1]. Although the relationship cannot be established from a single case, the reduction in globulin levels together with sustained clinical stability is consistent with a potential immunomodulatory effect of namodenoson.

Importantly, improvement in portal hypertension-related complications occurred despite progressive worsening of bilirubin, INR, and albumin. Therefore, the patient did not meet the concept of true recompensation; rather, the findings indicate a dissociation between clinical/hemodynamic improvement and continued loss of hepatic synthetic function. A3AR activation may preferentially influence inflammatory and vascular mechanisms while having limited capacity to reverse advanced architectural damage or hepatocellular failure.

The patient remained clinically stable for approximately 28 months and ultimately underwent successful orthotopic liver transplantation. This period of stability is meaningful in a patient with prior variceal haemorrhage, ascites, and progressive hepatic dysfunction, clinical features associated with poor transplant-free survival [1–3]. The observation raises the possibility that namodenoson could reduce selected decompensation-related complications and help maintain patients in suitable condition while awaiting transplantation.

In conclusion, namodenoson treatment was associated with improvement in portal hypertension-related complications, and the patient was successfully bridged to liver transplantation despite ongoing hepatic functional decline. This single-patient observation is hypothesis-generating and supports prospective evaluation of A3AR agonism as a potential supportive bridge-to-transplant strategy in decompensated cirrhosis.

5. Ethics Approval and Consent To Participate

The patient received namodenoson under a compassionate-use protocol after approval by the institutional drug committee of Soroka University Medical Centre and the Israeli Ministry of Health. The treatment and reporting were conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patient before treatment.

Consent for publication

The patient provided written informed consent for publication of this case report and the associated anonymized clinical data and figure. The manuscript contains no information that could reasonably identify the patient.

6. Credit Authorship Contribution Statement

David Yardeni: Data curation. Zivit Harpaz: Supervision. Ohad Etzion: Conceptualization; writing—review and editing. Pnina Fishman: Writing-original draft; writing-review and editing; validation. All authors reviewed and approved the final manuscript.

7. Funding

Can-Fite BioPharma Ltd. provided namodenoson for compassionate use and supported preparation of this manuscript. No separate external grant funding was received for this case report.

8. Declaration of Competing Interest

David Yardeni and Ohad Etzion declare no competing interests. Pnina Fishman is Chief Scientific Officer and Chairperson of Can-Fite BioPharma Ltd., and Zivit Harpaz is an employee of the company. Pnina Fishman and Zivit Harpaz hold options in Can-Fite BioPharma Ltd. Namodenoson is being developed by Can-Fite BioPharma Ltd.

9. Data Availability

The clinical data supporting this case report are contained within the article. Additional de-identified data may be available from the corresponding author on reasonable request, subject to patient confidentiality and applicable institutional and regulatory requirements.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT for language editing, including grammar, structure, spelling, punctuation, and formatting. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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