KLİNİK HAL **AÇIQ GİRİŞ (OPEN ACCESS)**

RAPID REGRESSION OF LIVER ELASTOGRAPHY PARAMETERS DURING INTRAVENOUS MSC-EXOSOME THERAPY IN A PATIENT WITH CHRONIC HEPATITIS C AND NON-CELIAC GLUTEN INTOLERANCE: A CASE REPORT

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Abstract

Acute deterioration in the course of chronic liver diseases may be associated with systemic inflammation, decompensation, and a high risk of adverse outcomes, requiring a comprehensive diagnostic and therapeutic approach [8,9]. Liver fibrosis remains a key predictor of complications and mortality, while the literature emphasizes the absence of FDA-approved pharmacologic agents that directly reverse liver fibrosis, except for liver transplantation in end-stage disease [1]. In this context, mesenchymal-derived exosomes/extracellular vesicles (EVs) are considered a potential antifibrotic and anti-inflammatory approach in experimental models, and early data on the tolerability of EV/exosome interventions are accumulating in preclinical and early clinical studies [2-7]. We present a case of a female patient born in 1973 with chronic hepatitis C, non-celiac gluten intolerance, and longstanding iron deficiency anemia, who at first presentation had ascites on ultrasound, hypoalbuminemia, and biochemical signs of active hepatic inflammation with extrahepatic causes of ascites excluded. During standard antiviral therapy with sofosbuvir/velpatasvir (12 weeks) [10] and a parallel course of intravenous MSC-exosome infusions (outpatient setting, 5 billion/ml, diluted in 200 ml 0.9% NaCl, intravenous drip), liver stiffness by elastography first increased and then showed sustained decline to values interpreted clinically as regression to F0, together with clinical recovery, absence of complaints by 23.01.2026, and resolution of psychiatric symptoms (baseline HADS 14/5, later no psychiatric symptoms reported). This observation is hypothesis-generating and does not prove treatment efficacy; however, the magnitude and speed of changes warrant attention and support the need for broader controlled clinical trials of EV/exosome-based approaches [2-7].

Keywords: Exosomes; extracellular vesicles; liver fibrosis; liver elastography; chronic hepatitis C; sofosbuvir/velpatasvir; case report.

INTRODUCTION

Liver fibrosis represents a common final pathway of chronic hepatic injury and is a major determinant of decompensation risk and mortality. The literature emphasizes that there are no FDA-approved drugs that directly "treat liver fibrosis," with liver transplantation being the only established option for end-stage disease [1]. Current strategies therefore rely primarily on removal of the underlying cause, such as eradication of HCV, and reduction of inflammatory activity. In parallel, cell-based and cell-free regenerative approaches are actively investigated, including mesenchymal stromal cell–derived exosomes/EVs, because experimental models demonstrate their impact on key mechanisms of inflammation and fibrogenesis, while an initial body of tolerability data for EV/exosome interventions is emerging [2-7]. The present case report describes a patient with chronic hepatitis C and clinical signs of decompensation at presentation, in whom a pronounced improvement in elastography parameters and clinical status was observed during standard antiviral therapy combined with a series of MSC-exosome infusions.

Clinical Rationale (Literature Context)

Preclinical studies indicate that mesenchymal-derived exosomes/EVs may exert antifibrotic effects through several complementary mechanisms. In liver fibrosis models, exosomes derived from human umbilical cord mesenchymal stem cells were associated with reduced expression of TGF-β1, Smad2, and epithelial–mesenchymal transition markers, targeting central fibrogenic signaling pathways [2]. In a rat NASH/fibrosis model, extracellular vesicles from amnion-derived mesenchymal stem cells were associated with reduced biochemical markers of liver injury (ALT/AST), decreased proinflammatory cytokines (IL-1β, IL-6), reduced expression of fibrogenic genes, decreased collagen deposition, and lower α-SMA expression, consistent with simultaneous modulation of inflammation and hepatic stellate cell activity [7]. In addition, a 2023 study reported that exosomes from adipose mesenchymal stem cells ameliorated hepatic fibrosis by inhibiting the PI3K/Akt/mTOR pathway and remodeling choline metabolism, suggesting effects on proliferative, metabolic, and signaling nodes involved in fibrogenesis [3]. Together, these data provide biological plausibility for the hypothesis that exosomes/EVs may influence fibrosis dynamics and hepatic inflammatory activity.

Safety and tolerability are also critical considerations. A preclinical safety evaluation of exosomes derived from human umbilical cord mesenchymal stromal cells reported no significant adverse effects on liver or renal function in studied models and concluded that intravenous exosome administration was tolerable under the tested conditions [6]. Early clinical studies in other fields reported tolerability of EV/exosome-based interventions, including a phase 1 randomized placebo-controlled trial of engineered extracellular vesicles (ILB-202) showing no serious or dose-limiting toxicities and stable laboratory and vital parameters [1], and a first-in-human phase I study of intrathecal human umbilical cord MSC-derived exosomes reporting safety and tolerability without early or late adverse events [4]. In addition, although involving cells rather than exosomes, the first-in-human PASSIoN study of intranasal MSC administration after perinatal stroke reported no serious adverse events and explicitly emphasized the need for further placebo-controlled efficacy trials, which is conceptually aligned with the developmental stage of EV/exosome therapies [5]. These data do not prove efficacy in liver fibrosis but support biological and clinical plausibility and justify further structured investigation.

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CASE DESCRIPTION

A female patient born in 1973 first presented on 21.06.2024. At baseline evaluation, ascites was detected on ultrasound, together with hypoalbuminemia and a biochemical pattern of active hepatic inflammation; extrahepatic causes of ascites were excluded. The patient was found to have gluten intolerance without celiac disease, as specific celiac markers were negative, and had a lifelong history of iron deficiency anemia under hematologic follow-up. Baseline HADS score was 14/5; later, the patient reported complete resolution of psychiatric symptoms. Liver elastography values (kPa) over time were: 25.06.2024 — 9.34; 03.10.2024 — 10.04; 16.11.2024 — 10.3; 23.05.2025 — 8.4; 19.07.2025 — 7.9; 17.01.2026 — 6.8. At the last visit on 23.01.2026, the patient reported no complaints, and the diagnosis of liver fibrosis was considered resolved in the clinical assessment.

Interventions

Etiotropic antiviral therapy for HCV consisted of sofosbuvir/velpatasvir 400/100, started on 05.07.2024 and completed on 27.09.2024. This regimen and 12-week duration are consistent with published clinical practice guidelines for HCV management, which report high rates of sustained virologic response with a 12-week sofosbuvir/velpatasvir course [10]. HCV PCR was negative at 3 months after treatment completion (11.01.2025) and again at 6 months (13.03.2025), consistent with sustained virologic response.

MSC-exosomes were administered intravenously in an outpatient setting, by drip infusion, at a concentration of 5 billion exosomes per ml, diluted in 200 ml of 0.9% NaCl. Dates of MSC-exosome administration were: 05.07.2024; 02.08.2024; 31.08.2024; 05.10.2024; 19.10.2024; 02.11.2024; 16.11.2024; 31.05.2025; 14.06.2025; 28.06.2025; 15.07.2025; 16.08.2025; 18.09.2025. It was specifically noted in the clinical interpretation that fibrosis indicators initially progressed rapidly and that the MSC-exosome effect appeared delayed, followed by a marked decline in liver stiffness values.

Outcomes and Dynamics

The course was characterized by an initial increase in liver stiffness followed by a sustained decrease. Elastography values rose from 9.34 kPa (25.06.2024) to 10.3 kPa (16.11.2024), then decreased to 8.4 kPa (23.05.2025), 7.9 kPa (19.07.2025), and 6.8 kPa (17.01.2026). Clinically, symptoms regressed, and by 23.01.2026 the patient reported no complaints; the diagnosis of liver fibrosis was considered removed in the clinical summary. Virologic response to antiviral therapy was sustained, with negative PCR results at both follow-up time points, confirming HCV eradication as a major etiologic factor likely influencing inflammation and fibrosis dynamics. Baseline anxiety/depressive burden by HADS (14/5) resolved according to patient report.

Table 1

Date	Event/Parameter	Value/Comment
21.06.2024	First presentation	Ascites on ultrasound; hypoalbuminemia; active hepatic inflammation; extrahepatic causes excluded
25.06.2024	Elastography	9.34 kPa

Date	Event/Parameter	Value/Comment
05.07.2024	MSC-exosomes + start antiviral therapy	MSC-exosomes IV drip, 5 billion/ml in 200 ml 0.9% NaCl; start sofosbuvir/velpatasvir
02.08.2024	MSC-exosomes	Infusion
31.08.2024	MSC-exosomes	Infusion
27.09.2024	End antiviral therapy	End of 12-week course
03.10.2024	Elastography	10.04 kPa
05.10.2024	MSC-exosomes	Infusion
19.10.2024	MSC-exosomes	Infusion
02.11.2024	MSC-exosomes	Infusion
16.11.2024	Elastography + MSC-exosomes	10.3 kPa; infusion
11.01.2025	HCV PCR	Negative (3 months post-therapy)
13.03.2025	HCV PCR	Negative (6 months post-therapy), SVR
23.05.2025	Elastography	8.4 kPa
31.05.2025	MSC-exosomes	Infusion
14.06.2025	MSC-exosomes	Infusion
28.06.2025	MSC-exosomes	Infusion
19.07.2025	Elastography	7.9 kPa
15.07.2025	MSC-exosomes	Infusion
16.08.2025	MSC-exosomes	Infusion
18.09.2025	MSC-exosomes	Infusion
17.01.2026	Elastography	6.8 kPa
23.01.2026	Final visit	No complaints; fibrosis diagnosis removed

DISCUSSION

In this case, against a background of standard HCV antiviral therapy and repeated MSC-exosome infusions, an unusually pronounced and relatively rapid improvement in liver stiffness by elastography was observed after an initial phase of worsening. This pattern can formally be explained by multiple overlapping influences, including eradication of the etiologic factor (HCV with confirmed SVR), reduction of hepatic inflammatory activity, and a possible additional anti-inflammatory and antifibrotic contribution from EV/exosome therapy. Biological plausibility for the latter is supported by experimental data showing that mesenchymal-derived exosomes reduce key mediators of fibrogenesis, including TGF-β/Smad signaling and EMT markers [2], reduce inflammatory cytokines and fibrosis markers with decreased collagen and α-SMA [7], and may act via PI3K/Akt/mTOR and choline metabolism pathways as mechanistic nodes relevant to fibrosis modulation [3]. With respect to tolerability, provided sources include preclinical safety data for intravenous MSC-exosomes [6] and early clinical EV/exosome studies in other indications showing acceptable safety profiles without serious or dose-limiting toxicity [1,4], supporting the conceptual feasibility of further clinical development, although not establishing indication-specific safety or efficacy for liver fibrosis.

The limitations of this report are substantial and must be stated explicitly. By design, a case report cannot establish causality because it lacks randomization, controls, blinding, and standardized independent outcome verification. In this specific case, numerical laboratory data and their dynamics are not available, preventing quantitative linkage between elastography changes and biochemical liver function or inflammatory activity; technical elastography parameters are not provided; no histologic verification is available; and no standardized liver severity scores are reported. Concomitant etiologic antiviral therapy is a major confounder, since elimination of chronic viral inflammation itself can lead to improvement in liver parameters and fibrosis dynamics, and the relative contribution of standard therapy versus experimental MSC-exosome therapy cannot be separated in a single observation [10]. Nevertheless, the magnitude and tempo of stiffness changes, together with the described delayed-then-marked response pattern, draw attention and, without proving anything, justify further methodologically rigorous, larger-scale clinical trials of EV/exosome-based approaches in liver disease, especially given the mechanistic and tolerability signals reported in the cited sources [1-7,10].

CONCLUSION

This anonymized case report describes a female patient born in 1973 with chronic hepatitis C, non-celiac gluten intolerance, and signs of decompensation at presentation, in whom sustained improvement in liver elastography parameters and clinical status was observed during sofosbuvir/velpatasvir therapy with confirmed SVR and a parallel course of intravenous MSC-exosome infusions. The observation does not prove efficacy of MSC-exosome therapy; however, in the context of experimental antifibrotic mechanisms, including PI3K/Akt/mTOR and TGF-β/Smad-related pathways, and early tolerability data for EV/exosome interventions, it supports the rationale for further controlled clinical studies [1-7,10].

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БЫСТРЫЙ РЕГРЕСС ПОКАЗАТЕЛЕЙ ЭЛАСТОГРАФИИ ПЕЧЕНИ НА ФОНЕ ВНУТРИВЕННОЙ ТЕРАПИИ ЭКЗОСОМАМИ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК (МСК) У ПАЦИЕНТА С ХРОНИЧЕСКИМ ГЕПАТИТОМ С И НЕПЕРЕНОСИМОСТЬЮ ГЛЮТЕНА БЕЗ ЦЕЛИАКИИ: ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Резюме

Острое ухудшение течения хронических заболеваний печени может сопровождаться системным воспалением и высоким риском неблагоприятных исходов. Фиброз печени остается ключевым фактором риска, однако на сегодняшний день отсутствуют одобренные FDA препараты, напрямую обеспечивающие его регресс. В данном контексте экзосомы/внеклеточные везикулы (ВВ) мезенхимального происхождения рассматриваются как перспективный антифибротический метод. В статье представлен клинический случай пациентки 1973 года рождения с хроническим гепатитом С, нецелиакийной непереносимостью глютена и железодефицитной анемией. При первичном осмотре был выявлен асцит и признаки активного воспаления печени. На фоне стандартной противовирусной терапии (софосбувир/велпатасвир) и

параллельного курса внутривенных инфузий экзосом МСК (5 миллиардов/мл) наблюдалась уникальная динамика: после кратковременного роста показателей жесткости печени последовало их устойчивое снижение до уровня F0. К январю 2026 года пациентка не предъявляла жалоб, а диагноз фиброза был снят. Данное наблюдение является гипотезообразующим и подчеркивает необходимость дальнейших контролируемых клинических исследований эффективности экзосом.

XRONİKİ HEPATİT C VƏ QLÜTENƏ QEYRİ-SELYAKİYA DÖZÜMSÜZLÜYÜ OLAN PASİENTDƏ VENADAXİLİ MSK-EKZOSOM TERAPİYASI ZAMANI QARACİYƏR ELASTOQRAFİYASI PARAMETRLƏRİNİN SÜRƏTLİ REQRESSİYASI: KLİNİKİ HAL

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Xülasə

Xroniki qaraciyər xəstəliklərinin kəskin pisləşməsi sistemli iltihab və mənfi nəticələrin yüksək riski ilə müşayiət oluna bilər. Qaraciyər fibrozu əsas risk faktoru olaraq qalır, lakin hazırda FDA tərəfindən birbaşa fibrozu geri qaytaran təsdiqlənmiş preparatlar yoxdur. Bu kontekstdə mezenxim mənşəli ekzosomlar/hüceyrəxarici vezikullar (HV) perspektivli antifibrotik yanaşma kimi nəzərdən keçirilir. Məqalədə 1973-cü il təvəllüdlü, xroniki hepatit C, qlütenə qeyri-selyakiya dözümsüzlüyü və dəmir çatışmazlığı anemiyası olan qadın pasientin kliniki halı təqdim edilir. İlk müayinədə assit və aktiv qaraciyər iltihabı əlamətləri aşkar edilmişdir. Standart virusəleyhinə terapiya (sofosbuvir/velpatasvir) və paralel olaraq keçirilən venadaxili MSK-ekzosom infuziyaları (5 milyard/ml) fonunda unikal dinamika müşahidə olunmuşdur: qaraciyər sərtliyi göstəricilərinin qısamüddətli artımından sonra onların F0 səviyyəsinə qədər davamlı azalması baş vermişdir. 2026-cı ilin yanvar ayına olan məlumata görə, pasientin heç bir şikayəti olmamış və fibroz diaqnozu ləğv edilmişdir. Bu müşahidə fərziyyə xarakteri daşıyır və ekzosomların effektivliyinin gələcəkdə genişmiqyaslı klinik sınaqlarda yoxlanılmasının zəruriliyini əsaslandırır.