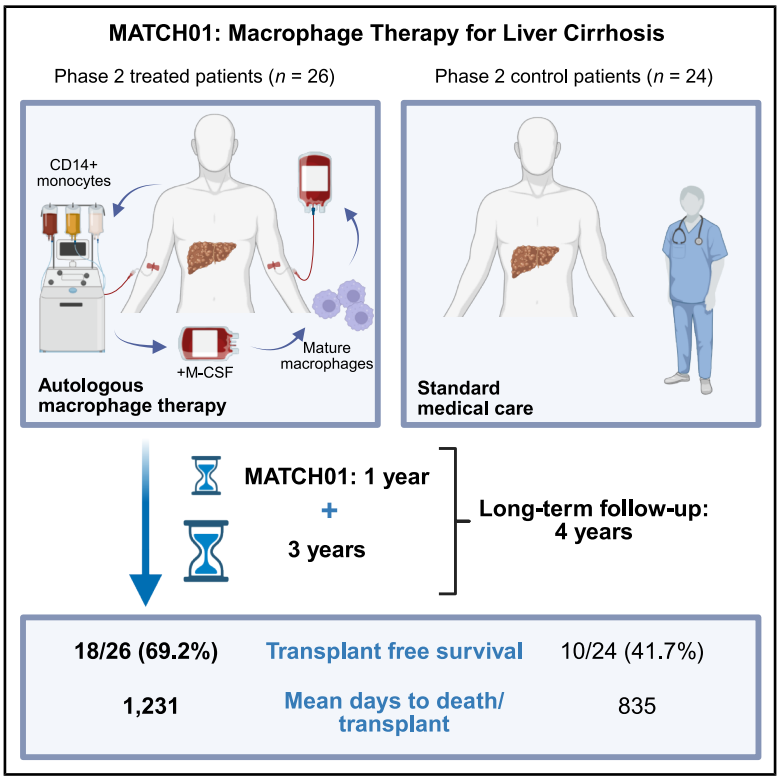
Cell Stem Cell

Clinical and Translational Report

Autologous macrophage therapy increases transplant-free survival in cirrhosis: Long-term follow-up of a phase 2 clinical trial

Graphical abstract



Highlights

- Cirrhosis patients were treated with autologous macrophages vs. standard care
- Macrophage-treated patients had significantly prolonged transplant-free survival
- No evidence of increased serious adverse events attributable to macrophage therapy
- Stabilization of proinflammatory cytokines was associated with improved long-term survival

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In brief

Brennan and Kilpatrick et al. report long-term outcomes in patients with cirrhosis treated with autologous monocyte-derived macrophage therapy. Macrophage-treated patients demonstrated a significantly reduced risk of death or transplant at 4 years. Favorable safety and tolerability support further evaluation of macrophage-based therapy as a potential treatment option.

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Clinical and Translational Report

Autologous macrophage therapy increases transplant-free survival in cirrhosis: Long-term follow-up of a phase 2 clinical trial

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SUMMARY

Liver cirrhosis is a major contributor to global morbidity and mortality, and transplantation remains the only cure for end-stage disease. Preclinical studies have indicated that macrophage injections reduce inflammation, resolve fibrosis, and stimulate liver regeneration. The phase 1/2 Macrophage Therapy for Liver Cirrhosis trial (MATCH01; ISRCTN10368050) demonstrated the safety and potential efficacy of autologous monocyte-derived macrophage therapy in cirrhosis. Following MATCH01, participants were re-enrolled in a long-term follow-up (LTFU) study, extending observation to up to 4 years from randomization. Macrophage-treated patients in MATCH01 phase 2 demonstrated a significantly lower risk of death or transplant within the LTFU period (30.8%) compared with standard medical care (58.3%); macrophage-treated patients had an additional 252 days of restricted mean survival time within the LTFU period. There was no evidence of increased serious adverse events attributable to cell therapy. These results support the continued advancement of macrophage-based regenerative strategies as a promising therapeutic option for end-stage liver disease.

INTRODUCTION

Cirrhosis represents a major global health burden, with substantial and rising morbidity and mortality.[1] Apart from liver transplantation, therapeutic options for end-stage disease remain limited to supportive care and management of complications, underscoring the urgent need for innovative approaches to halt or reverse disease progression.[2]

The onset of acute decompensation, or acute-on-chronic liver failure, in patients with decompensated advanced chronic liver disease (dACLD) marks a critical inflection point in the natural history of cirrhosis, associated with a significantly increased risk of morbidity and mortality.[3] Therefore, preserving patients in the compensated stage of ACLD, or achieving "recompensation" of decompensated cirrhosis, is a key therapeutic goal with substantial clinical benefit.[4,5]

In mice with experimental liver fibrosis, infusion of syngeneic macrophages reduced liver inflammation and fibrosis, stimulated liver regeneration, and improved liver synthetic function.[6] Injection of human macrophages into immunodeficient mice conferred similar effects.[7] Moreover, monocytes from patients with cirrhosis can be differentiated into macrophages with a similar pro-resolution phenotype to macrophages from healthy controls, indicating their suitability for clinical therapy.[7] Consistent with these findings, macrophages derived from embryonic stem cells have also been shown to ameliorate liver fibrosis in a murine liver injury model.[8] In addition, alternatively activated macrophages (AAMs) accelerate clearance of necrotic tissue and promote repair following acute liver injury,[9] further supporting a role for reparative macrophage phenotypes in hepatic regeneration and resolution of injury.

The Macrophage Therapy for Liver Cirrhosis (MATCH01) phase 1/2 trial evaluated the safety and efficacy of autologous monocyte-derived macrophages (MDMs) in patients with compensated cirrhosis (ISRCTN10368050). The phase 1 single-center dose-escalation component demonstrated the safety and feasibility of peripherally infused autologous macrophages.[10] The primary outcome of the subsequent multicenter,

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phase 2 randomized controlled study was the difference in the change from baseline to day 90 in model for end-stage liver disease (MELD) score (ΔMELD) between patients with compensated cirrhosis treated with macrophage therapy and standard medical care (ΔΔMELD). Although the ΔΔMELD missed statistical significance (p = 0.06), there was a trend toward improvement with cell therapy.[11,12]

Following MATCH01, a long-term follow-up (LTFU) study was initiated in the patient groups from both the phase 1[10] and the phase 2[11] study to evaluate the durability of therapeutic benefit and monitor adverse events for 4 years post-randomization, using routinely collected clinical data. Although not prespecified in the original trial design, this extension provides important and unique insights into the natural history of patients with compensated cirrhosis who participated in a novel cell therapy trial. This final analysis, reporting long-term outcomes of MATCH01, supports the potential of macrophage therapy in advanced liver disease.

RESULTS

Autologous macrophage therapy increases transplant-free survival in patients with liver cirrhosis

Mortality and transplantation data in MATCH01 phase 2 patients were complete for the full LTFU period. We recorded 9 deaths and 5 transplants (combined n = 14/24; 58.3%) in the control group and 8 deaths and no transplants (n = 8/26; 30.8%) in cell-treated patients (Tables 1 and 2; Figure 1A). We recorded one death and no transplants in phase 1 patients (n = 9) within the LTFU period (Table S1). Although the mortality rate 4 years post-treatment was higher in phase 2 cell-treated patients compared with phase 1, the difference was not statistically significant due to low patient numbers, especially in phase 1 (p = 0.39).

Survival analysis of phase 2 patient data using a Cox proportional hazards model with composite endpoint gave a hazard ratio (HR) for death or transplant in cell-treated patients, compared with the control group, of 0.39 (95% confidence interval [CI], 0.16–0.94; p = 0.035) (Figure 1B). Testing for the proportional hazards assumption with Schoenfeld residuals indicated no significant change in HR over time (p = 0.17) (Figure S1). Median time to event was 1,230.5 days in cell-treated patients and 834.5 days in the control group.

In a Fine-Gray model of mortality, with transplant as a competing risk, the subdistribution hazard ratio (SHR) for mortality in cell-treated patients compared with the control group was 0.69 (95% CI, 0.27–1.74; p = 0.43) (Figure 1C). Median time to death was 1,230.5 days in cell-treated patients (as above) and 790 days in the control group. The difference in restricted mean survival time (RMST; mean event-free time within follow-up) between groups within the follow-up period was 252 days (95% CI, 76–433 days, p = 0.006); the ratio of RMST between groups was 1.23 (95% CI, 1.06–1.45; p = 0.006). The restricted mean time lost (RMTL) ratio was 0.28 (95% CI, 0.09–0.65; p = 0.004).

Given that death and transplant were competing endpoints, we explored the history of patients who died in the treatment cohort to understand whether transplantation may have been a realistic option. Of these individuals, two patients had multifocal hepatocellular carcinoma (HCC) and were thus outside typical transplant criteria, one individual died by drowning, and five individuals succumbed to sequelae of decompensated disease. Of the five who had decompensated cirrhosis, one individual was ineligible due to a return to hazardous alcohol consumption, while three patients had advanced age or co-morbidities that precluded transplantation.

We also sought to investigate the rate of liver-related mortality in phase 2 cell-treated patients (n = 7/8), which was higher than in control patients (n = 4/9), although not significantly so (p = 0.13; Table 1). The competing outcomes for individuals within these

Table 1. Overview of deaths in MATCH01 phase 2 patients within the LTFU period

Patient	Etiology of liver disease	Cause of death	Age at death (years)	Liver-related (yes/no)
Cell-treated				
1	ArLD	dACLD- HE	70	yes
2	MASLD/ HFE	multifocal HCC	68	yes
3	ArLD	dACLD—GIB/HE	57	yes
4	ArLD	multifocal HCC; dACLD	65	yes
5	MASLD	dACLD; sepsis (cellulitis)	72	yes
6	ArLD	dACLD—multiorgan dysfunction	68	yes
7	ArLD	accidental drowning	47	no
8	MASLD	dACLD—ascites/HE	73	yes
Control				
1	ArLD	dACLD—SARS2-CoV pneumonitis	76	yes
2	ArLD	dACLD; sepsis, hepatic hydrothorax	57	yes
3	MASLD	disseminated lymphoma; ESLD	72	no
4	ArLD	dACLD—HE; multiorgan dysfunction; colon cancer	66	yes
5	ArLD	esophageal neoplasia	72	no
6	ArLD	dACLD—HE, ascites; anoxic brain injury; DIC—sepsis	49	no
7	MASLD	dACLD—HE	68	yes
8	ArLD	cardiopulmonary arrest; PE	55	no
9	MASLD	SARS-CoV2 pneumonitis; cardiac failure	55	no

ArLD, alcohol-related liver disease; dACLD, decompensated advanced chronic liver disease; DIC, disseminated intravascular coagulopathy; ESLD, end-stage liver disease; GIB, gastrointestinal bleed; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HFE, hemochromatosis; MASLD, metabolic dysfunction-associated steatotic liver disease; PE, pulmonary embolus.

Table 2. Overview of relevant indications for transplant in MATCH01 phase 2 patients within the LTFU period

Patient	Etiology of liver disease	Age at randomization (years)	Days randomization to transplant	MELD	MELD3.0	UKELD	Referral criteria
Cell-treated							
1	MetALD	65	833	14	15	53	disease progression
2	ArLD	56	902	14	17	54	disease progression
3	PBC	58	1,009	13	17	52	disease progression
4	PBC	63	1,377	20	24	57	disease progression
5	cryptogenic cirrhosis	56	1,442	14	28	55	disease progression

Indications are based on etiology and listing criteria. MELD, MELD3.0, and UKELD were computed at the time of listing for transplant. Referral criteria for all patients were disease progression to standard listing criteria, with no contraindications to transplant. ArLD, alcohol-related liver disease; MELD, model for end-stage liver disease; MELD3.0, model for end-stage liver disease 3.0; MetALD, metabolic dysfunction-associated alcohol-related liver disease; UKELD, United Kingdom model for end-stage liver disease; PBC, primary biliary cholangitis.

groups were death and transplantation. However, it is not possible to fully account for why an individual may not be offered transplantation as a life-saving intervention, given the specific clinical and patient characteristics that influence this decision. Therefore, for those ineligible for transplantation (e.g., due to clinical frailty or advanced age, as discussed above), transplantation is not a viable option, and apparent survivor bias results in death from liver-related events (LREs) being the most common form of mortality among those with recent decompensation (Table S2).[13,14]

Autologous macrophage therapy shows no long-term increase in serious adverse events

To assess the long-term safety of the autologous macrophage therapy administered in MATCH01, we analyzed data on hospitalizations and HCC incidence. We recorded n = 15 hospitalizations (n = 5 liver related) in n = 10 cell-treated phase 2 patients, and n = 16 (n = 4 liver related) hospitalizations in n = 9 control group patients within the LTFU period (Table S2). The median time to first hospitalization was 1,088 days in cell-treated patients and 572 days in control patients; the median time to first

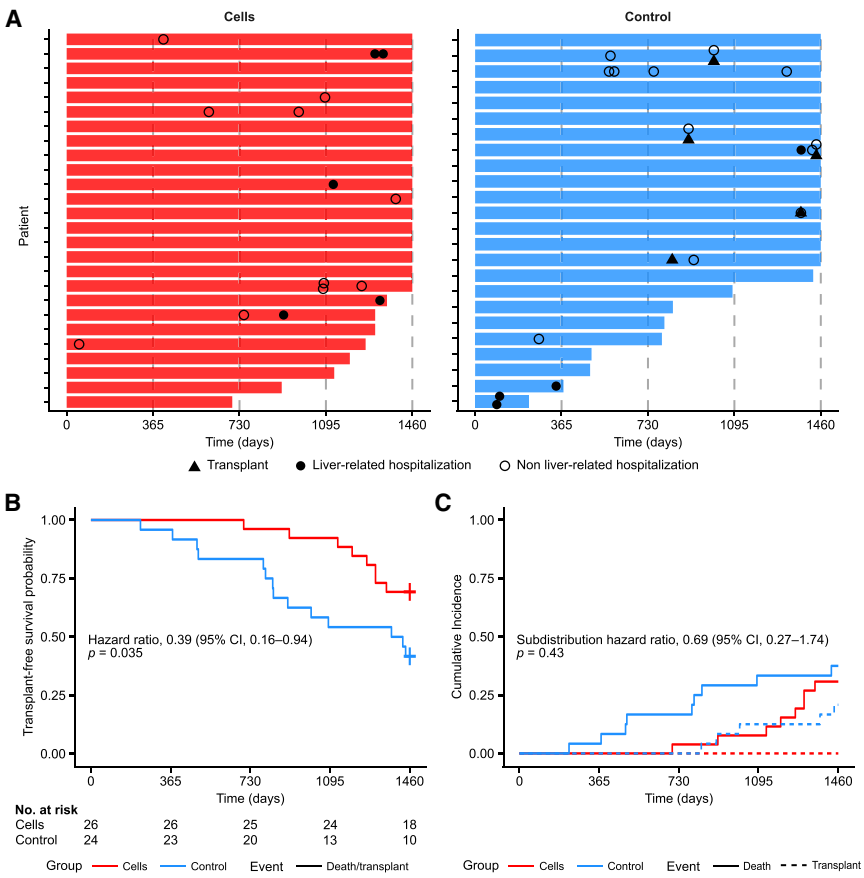


Figure 1. Autologous macrophage therapy increases transplant-free survival in patients with liver cirrhosis

(A) Swimmer plot of MATCH01 phase 2 patients, stratified by treatment group (n = 26 cell-treated patients; n = 24 control); transplant and hospitalization dates are indicated for each patient.

(B) Kaplan-Meier estimates of time from randomization to 4 years for the composite endpoint of death or transplant. p = 0.035 by Cox proportional hazards regression (Wald test). (C) Cumulative incidence functions for patient mortality, with transplant as a competing risk. p = 0.43 by Fine-Gray competing risks regression (Wald test).

See also Figure S1.

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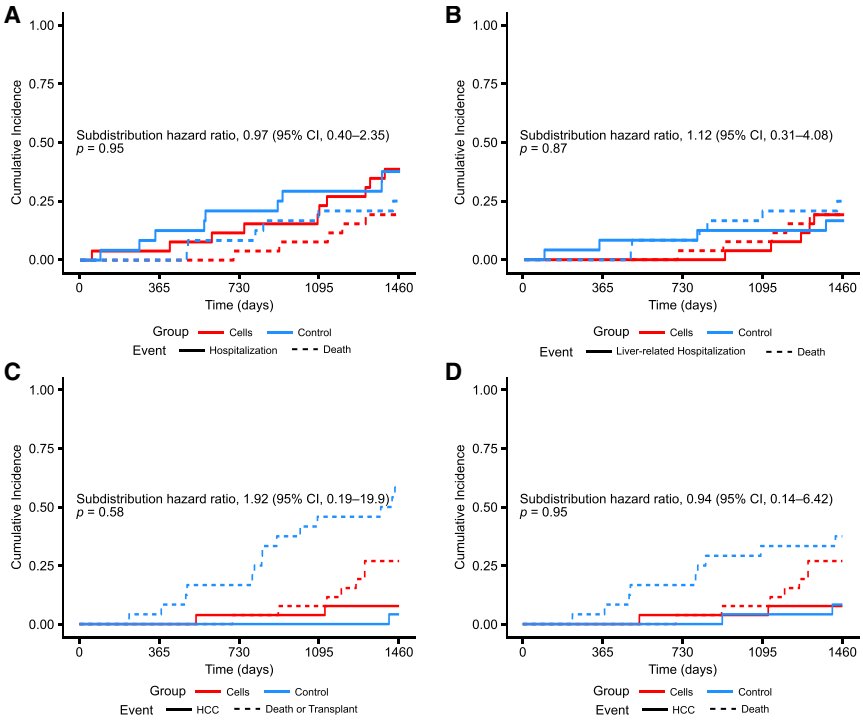


Figure 2. Autologous macrophage therapy shows no long-term increase in serious adverse events

Cumulative incidence functions stratified by treatment group for: (A) hospitalization for any reason, with death as a competing risk; $p = 0.48$. (B) Liver-related hospitalization, with death as a competing risk; $p = 0.20$.

(C) Hepatocellular carcinoma (HCC) with death or transplant as composite competing risks; $p = 0.58$.

(D) HCC with death as the sole competing risk; $p = 0.95$. All p values by Fine-Gray competing risks regression (Wald test).

liver-related hospitalization was 1,215 and 343 days, respectively.

Modeling hospitalization for any reason with mortality as a competing risk indicated a non-significant SHR of 0.97 in cell-treated patients compared with the control group (95% CI, 0.40 to 2.35; $p = 0.95$) (Figure 2A). Modeling liver-related hospitalizations indicated an SHR of 1.12 in cell-treated patients; again, this was non-significant (95% CI, 0.31 to 4.08; $p = 0.87$) (Figure 2B).

The rate of all hospitalizations in control patients was 0.62 admissions per patient-year (95% CI, 0.28 to 1.40). Negative binomial regression modeling adjusted for follow-up time estimated a similar hospitalization rate in cell-treated patients (rate ratio 0.64, 95% CI, 0.21 to 1.96, $p = 0.41$). Liver-related hospitalizations in control patients were rare (0.16 admissions per patient-year). This rate was similar in cell-treated patients (rate ratio 0.74, 95% CI, 0.12 to 4.84; $p = 0.73$).

We recorded $n = 5$ hospitalizations in $n = 2$ phase 1 patients within the LTFU period (Table S3). We note that four of these hospitalizations were for one patient; this broadly fits with our phase 2 data, which suggests that one hospitalization is often indicative of further hospitalizations.

Considering both deaths and transplants as competing risks, the cumulative incidence of HCC at 4 years in MATCH01 phase 2 patients was 7.7% ($n = 2/26$) in the treated group and 4.2% ($n = 1/24$) in controls ($p = 0.59$). The cumulative incidence of competing risks was 26.9% in treated patients and 58.3% in the control group ($p = 0.016$). Regression with deaths and transplants as a composite competing risk factor estimated a 92% higher subdistribution hazard of HCC incidence in cell-treated patients, although this effect was not significant (SHR 1.92; 95% CI, 0.19–19.9; $p = 0.58$) (Figure 2C).

Considering mortality as the sole competing risk, the cumulative incidence of HCC was 7.7% ($n = 2/26$) in the cell-treated group and 8.3% ($n = 2/24$) in the control group ($p = 0.95$); one of the two patients in the cell-treated group later died. The cumulative incidence of competing risks was 26.9% in cell-treated patients and 37.5% in the control group ($p = 0.30$). Regression with mortality as a competing risk factor estimated a 6% lower subdistribution hazard of HCC incidence in cell-treated patients compared with controls; however, this effect was not statistically significant (SHR 0.94; 95% CI, 0.14–6.42; $p = 0.95$) (Figure 2D).

Overall, there was no statistically significant difference in HCC incidence between groups under any competing-risk definition. No patients developed HCC in the phase 1 cohort.

Long-term ΔMELD and ΔUKELD outcomes are comparable across both phase 2 trial arms

ΔMELD data from randomization to day 360 in MATCH01 phase 2 were published previously.[11] Blood test data were available for the rest of the LTFU period in $n = 19$ cell-treated patients and $n = 15$ control group patients. These patients had sufficient data to compute MELD and United Kingdom end-stage liver disease (UKELD) scores at a median of 3 time points between 1 and 4 years (range 1–5, mean 3.13), with a final time point median of 1,335 days from randomization (range 820–1,457, mean 1,281).

Modeling ΔMELD trajectory to the point of death or transplant showed no significant difference between treatment groups over the LTFU period ($p = 0.76$; Figure 3A). Both groups showed non-significant trends for ΔMELD to increase over the LTFU period (cell-treated: +0.17/year, $p = 0.051$; control: +0.22/year, $p = 0.071$). We also computed estimated marginal means (EMMs) across groups at yearly intervals; at all tested time points, there was no significant divergence in ΔMELD between groups (all $p > 0.43$; Figure 3B).

There was no significant difference in ΔUKELD trajectory between treatment groups over the LTFU period ($p = 0.51$; Figure 3C). Both groups showed a trend for ΔUKELD to increase over the follow-up period; this was significant in cell-treated patients (+0.22/year, $p = 0.040$; control: +0.10/year, $p = 0.49$). Comparing divergence in ΔUKELD at yearly time points by

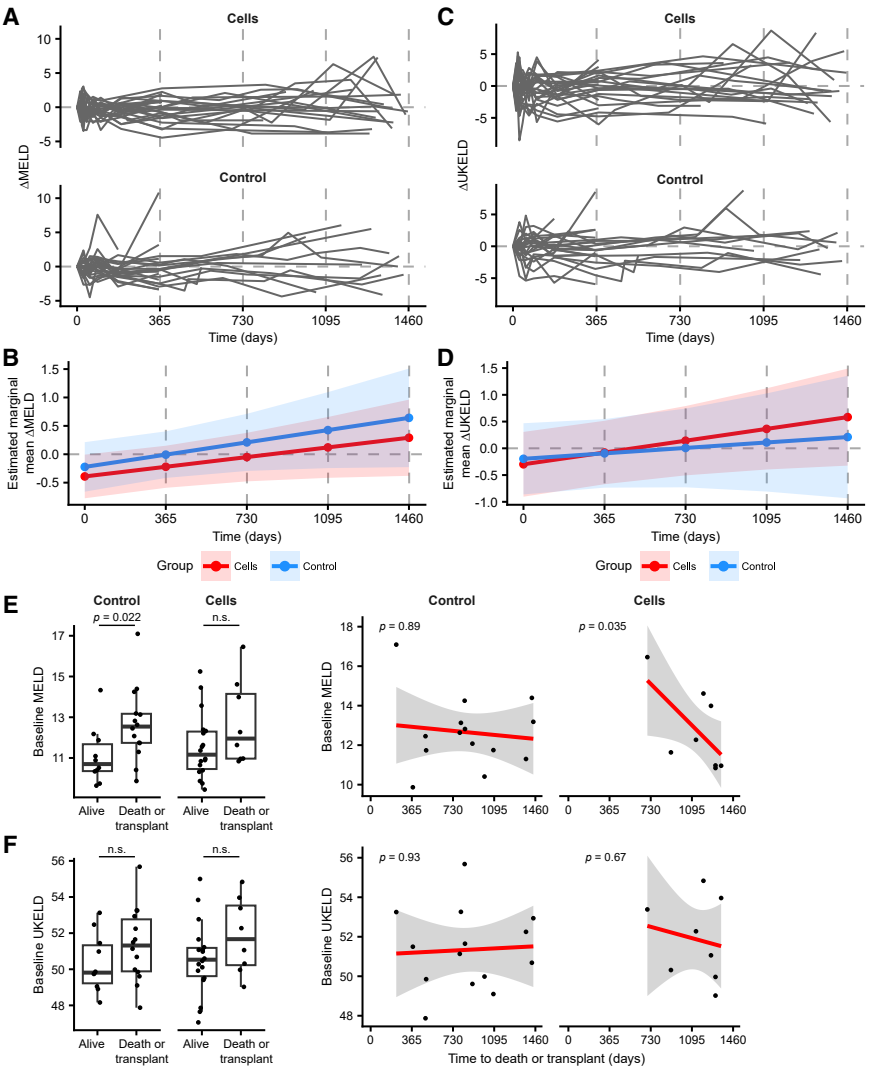


Figure 3. Long-term ΔMELD and ΔUKELD outcomes are comparable across both phase 2 trial arms

(A and C) Individual trajectories of ΔMELD and ΔUKELD scores in MATCH01 phase 2 patients.

(B and D) EMM ΔMELDs and ΔUKELDs in MATCH01 phase 2 patients, computed at yearly intervals. 95% CIs are shown.

(E) Boxplots of MATCH01 phase 2 patient baseline MELD, stratified by patient status for the composite death + transplant endpoint, at the end of the LTFU period; *p* values by Mann-Whitney test (left); correlation of days to death or transplant with baseline MELD; *p* values by Spearman rank correlation test; n.s., non-significant (right).

(F) As (E), for baseline UKELD.

See also Figure S2.

EMMs suggests an increasing but non-significant divergence between treatment groups over time (all $p > 0.61$; Figure 3D).

We observed a trend of increased baseline MELD and UKELD in phase 2 patients who died or received transplants, which was significant for MELD in control patients ($p = 0.022$; Figure 3E). We also observed a significant negative correlation between the days to death and baseline MELD in cell-treated patients ($p = 0.035$; Figure 3E). We observed similar but non-significant trends with respect to baseline UKELD (all $p >= 0.19$; Figure 3F). Although these observations are perhaps not unexpected, we caution against overinterpreting these results due to low patient numbers. Similar trends were observed when considering mortality as the sole endpoint (Figures S2A and S2B).

Phase 1 patient bilirubin, international normalized ratio (INR), and creatinine were assessed at 360 days post-randomization. Three patients had missing sodium measurements; therefore, UKELD could not be calculated for these patients. Three patients had no blood measurements after day 360. Of the remaining patients, there was sufficient blood data to compute MELD and UKELD at a median of 4 time points from 1 to 4 years (range 3–5, mean 4.17), with the final time point at a median of 1,339 days from randomization (range 1,170–1,421, mean 1,316).

Analysis of the phase 1 data showed no significant difference in ΔMELD trajectory by treatment dose over the follow-up period ($p > 0.28$ for all interactions; Figure S2C). All dosing groups showed trends for ΔMELD to increase slightly over the follow-up period, and these increases rose with escalating dose; however, all were non-significant (10^7: +0.0035/year, $p = 0.99$; 10^8: +0.052/year, $p = 0.71$; 10^9: +0.33/year, $p = 0.17$). As in our phase 2 analysis, EMMs at yearly intervals again indicated no significant divergence in ΔMELD between dosing groups (all $p > 0.36$).

Phase 1 data showed no significant difference in ΔUKELD trajectory by treatment dose ($p > 0.08$ for all interactions; Figure S2D). We observed non-significant trends for ΔUKELD to increase slightly in the highest two dosing groups (10^8: +0.31/year, $p = 0.091$; 10^9: +0.29/year, $p = 0.36$) and decrease slightly in the 10^7 dosing group (−0.22/year, $p = 0.37$). EMMs at yearly intervals suggest a divergence in ΔUKELD between the 10^7 and 10^8 dosing groups from 3 years onward (1,095 days, $p = 0.026$; 1,460 days, $p = 0.021$); however, the small sample sizes preclude robust conclusions.

Post-treatment upregulated proinflammatory cascades are associated with poorer long-term survival

We hypothesized that sustained clinical benefit following macrophage therapy correlates with effective control of systemic inflammation in the first 90 days post-administration. Proinflammatory cytokine measurements from MATCH01 phase 2 patients during the first 90 days post-treatment were categorized as increasing (≥10% relative to baseline), decreasing (≤10%), or unchanged and stratified by survival status at the end of the LTFU period (see STAR Methods).

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Analysis comparing control and macrophage-treated patients, stratified by patient survival, identified only modest differences in the distribution of cytokine responses. We observed a significant difference only in interleukin 7 (IL-7) among surviving patients at day 90, where the proportion of patients with increased IL-7 was higher in cell-treated survivors compared with survivors in the control group (cell-treated: n = 12/15; control: 1/14; p = 8.36E−4) (Figures S3A and S3B).

Our analysis suggested that among macrophage-treated phase 2 patients, rising proinflammatory cytokine levels were associated with poorer survival (Figure 4A). For example, the proportion of patients with increased tumor necrosis factor α (TNF-α) was consistently higher in non-survivors than in survivors across all time points (day 7: n = 3/8, 37.5% vs. n = 3/14, 20.0%; day 28: n = 4/8, 50% vs. n = 5/15, 33.3%; day 90: n = 6/8, 75.0% vs. 4/15, 26.7%, $p \geq 0.12$) (Figure 4B). Computing correlations of cytokine category proportions and clustering based on correlation distance indicated cytokines with similar and complementary patterns (Figures S3C and S3D). IL-2 was strongly correlated with TNF-α (R = 0.78, p = 0.013); similarly, the proportion of patients with increased IL-2 was consistently higher in non-survivors, significantly so at day 7 (n = 6/8, 75.0% vs. n = 3/13, 23.1%; day 28: n = 4/8, 50.0% vs. n = 4/14, 28.6%; day 90: n = 5/7, 71.4% vs. 5/14, 35.7%, $p \geq$ 0.043) (Figure 4B). IL-4 was strongly negatively correlated with IL-2 (R = −0.69, p = 0.041); the proportion of patients with decreased IL-4 was consistently higher in non-survivors (day 7: n = 4/8, 50.0% vs. n = 4/13, 30.8%; day 28: n = 6/8, 75.0% vs. n = 4/12, 33.3%; day 90. n = 5/8, 62.5% vs. 5/13, 38.5%, $p \geq$ 0.19) (Figure 4B).

Protein-protein interaction analysis confirmed coexpression of both TNF-α and IL-2 with IL-4 (Figure S3E), with significant enrichment of the immune response Gene Ontology (GO) term (false discovery rate [FDR] = 0.028). Extended analysis, including immediate interactors of these three cytokines, suggested potential roles for immunoglobulin-mediated immune response and modulation of the Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway (Figure S3F). Additional GO analysis also identified TNF-α, IL-2, and IL-4 as being involved in the adaptive immune response, specifically in the positive regulation of this response (Data S1).

Albumin, a serum marker of liver synthetic function, was analyzed in a similar manner to the cytokines above. The proportion of patients with decreased albumin relative to baseline was higher in non-survivors than in survivors at day 90 (n = 5/8, 62.5% vs. n = 5/15, 33.3%, p = 0.27); this proportion was higher 360 days post-treatment (n = 6/8, 75.0% vs. n = 4/15, 26.7%, p = 0.12) (Figure 4C).

Cell-treated patients were administered macrophages at the maximum yielded cellular concentration, up to a maximum of 1×10^9 cells, with a pre-defined minimum cell concentration of 1.25×10^8 cells.[11] Given the dosing variability driven by the autologous nature of the macrophage cell therapy, we sought to investigate whether the administered dose of manufactured cells affected cytokine levels within the first 90 days. We found no significant correlation between cell dose and log fold change of cytokine expression relative to baseline for any cytokine at any time point (all $p > 0.25$; Figure S3G). Although we observed some correlations with significant nominal p values, these were not robust to correction for multiple hypothesis testing.

Manufacturing variability of autologous cells did not affect long-term survival

As noted above, autologous macrophage therapy introduces variability in the manufactured cell product between patients. We therefore sought to further assess differences in quality, phenotype (as assessed by cell surface markers CD206, CD163, and CD169), or dose of manufactured cells as factors influencing long-term patient survival in MATCH01 phase 2 data; quality measures were stratified based on patient survival status at the end of the LTFU period (see STAR Methods). Macrophage manufacturing quality data were complete for all cell-treated patients, except for CD163 (n = 17/26, 65.4%) and CD169 (n = 18/26, 69.2%). We found no significant difference in macrophage yield percentage (p = 0.86) between surviving and non-surviving patients. We also found no difference in macrophage phenotype at manufacturing day 7 compared with baseline between survivors and non-survivors, with similarly high levels of scavenger receptors CD206 and CD163, as expected (CD206: p = 0.74; CD163: p = 0.94; CD169: p = 0.49) (Figures 5A and 5B). We additionally found no significant difference in macrophage dose, either as total cells administered (p = 0.38) or normalized to patient mass (dose/kg; p = 0.73) (Figures 5C and 5D). Although further high-throughput analysis of manufactured cells in future studies would be required to definitively exclude cell attributes correlating with long-term clinical outcomes, these findings reinforce our previous observation of no clear dose-specific effect on baseline to day 90 ΔMELD.[11]

DISCUSSION

Although cirrhosis prevalence and mortality rates continue to rise globally, with a >50% increase in cases since 1990,[15] treatment options beyond liver transplantation remain limited.[11] Additionally, many patients referred for liver transplant assessment are ineligible, while others die while on the waiting list (approximately 12% annually in the UK).[16]

The MATCH01 LTFU data presented here indicate that autologous MDM therapy confers a significant reduction in death or transplant (61%) in patients with compensated cirrhosis within 4 years of treatment compared with standard medical care. Transplant-free survival is an endpoint subject to variability related to external factors, including organ- and patient-specific as well as system-level constraints, such as allocation prioritization, blood group compatibility or donor-recipient matching considerations, and the availability or suitability of an organ for a particular individual, in addition to clinician-dependent transplant decision making. This latter concern was mitigated in MATCH01 by the rigorously regulated, multidisciplinary nature of transplant listing (governed by objective criteria and national allocation systems) in a single national transplant center. As transplants were carried out to prevent mortality, and 1-year post-transplant survival is high,[17] we also analyzed patient mortality in isolation, accounting for transplant as a competing risk. This suggested a smaller, non-significant reduction in the subdistribution hazard of death in treated patients; however, macrophage therapy was associated with a significant increase in

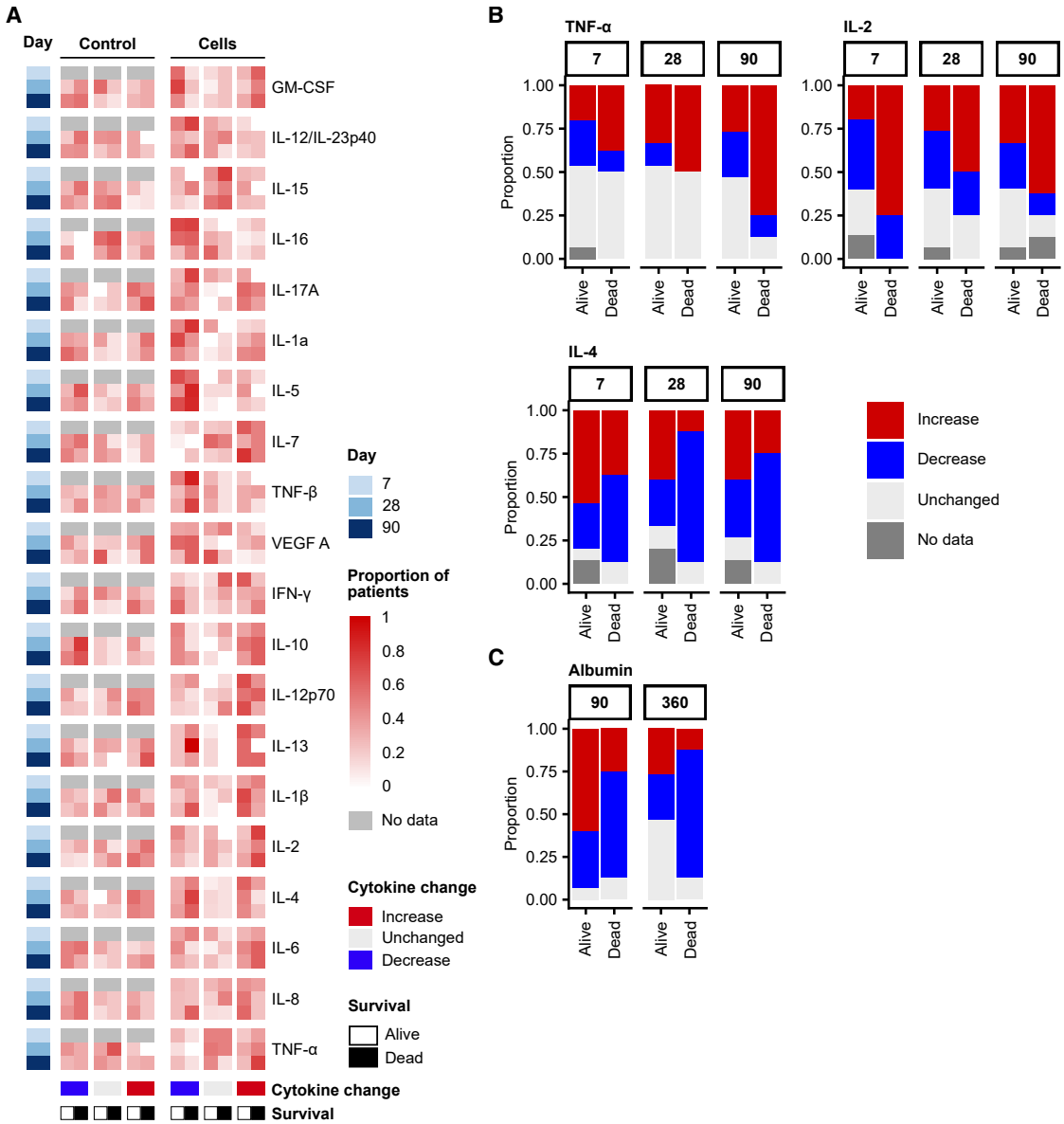


Figure 4. Post-treatment upregulated proinflammatory cascades are associated with poorer long-term survival

(A) Summary heatmap of cytokine changes in MATCH01 phase 2 patients at days 7, 28, and 90, relative to baseline. Patients are stratified by treatment group; cytokine changes are stratified as "increased," "unchanged," or "decreased" from baseline. Within each group, patients are stratified based on their survival status at the end of the LTFU period.

(B and C) Proportion of changes in TNF-α, IL-2, IL-4, and albumin in cell-treated patients, stratified by survival status at the end of the LTFU period.

See also Figure S3.

average survival of over 8 months within the 4-year follow-up period compared with standard care. Importantly, in this study, we report findings in relation to composite clinical endpoints to evaluate the potential clinical utility of autologous macrophage therapy. These include clinically meaningful outcomes such as reductions in LREs, liver transplantation, and mortality, which represent hard clinical endpoints. Such endpoints are widely accepted by regulatory authorities, including the US Food and Drug Administration (FDA),[18] for the evaluation of therapeutic benefit and are generally considered more clinically meaningful than changes in surrogate markers such as MELD score or liver stiffness measurements.

Although we have included data for individuals from the phase 1 trial, it should be noted that this study was focused on safety and feasibility, and outcomes were entirely exploratory. Furthermore, the cell doses administered were variable, and there was no control population; therefore, no significant causal associations should be inferred from these data.

Long-term safety of macrophage therapy was a critical focus of the current study. During follow-up, no adverse events were

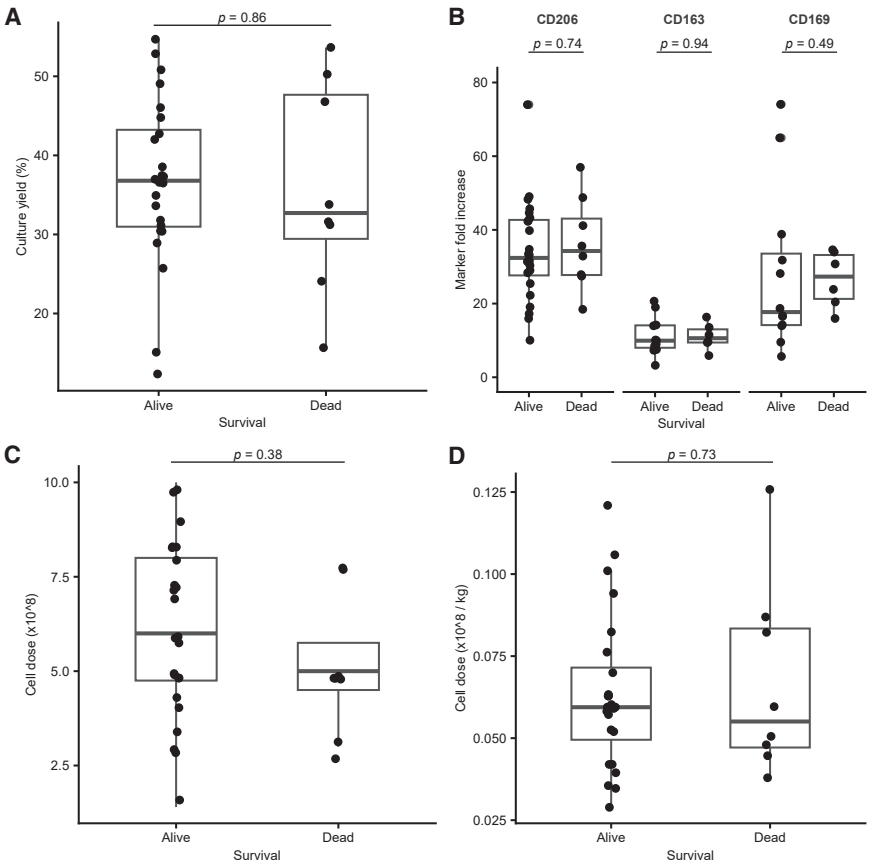


Figure 5. Manufacturing variability of autologous cells did not affect long-term survival

(A) Macrophage culture yield percentage for MATCH01 phase 2 patients.

(B) Fold increase in minimum fluorescence intensity of CD206, CD163, and CD169 at day 7 compared with day 0.

(C) Total cell dose.

(D) Cell dose, normalized to patient weight. All analyses were stratified by patient survival status at the end of the LTFU period. *p* values by Student's *t* test (except B, CD169, Mann-Whitney test).

identified that were directly attributable to the cell therapy, beyond those expected in patients with pre-existing cirrhosis. There was also no evidence that macrophage treatment increased the risk of hospitalization or HCC incidence under any competing risk definition. However, given the small number of HCC cases observed, these findings should be interpreted cautiously. Although definitive conclusions regarding safety cannot be drawn, the absence of treatment-related long-term complications, and the good tolerability observed, support the feasibility of macrophage therapy as a potentially safe treatment option for patients with cirrhosis.

ΔMELD predicts 3-month mortality in cirrhosis.[19] There was no significant difference in ΔMELD trajectory between treatment groups over the LTFU period; however, we note the potentially confounding effect of incomplete or truncated data (due to either a lack of data within the follow-up period, patient deaths, or transplants). We observed sustained stabilization in liver function among macrophage-treated patients following completion of MATCH01. The observed difference in ΔUKELD trajectory was statistically significant, but small (0.22 points/year), and unlikely to be clinically meaningful.

Given the observational design of the LTFU extension, during which patients returned to routine clinical care, it was not feasible to systematically collect measurements of fibrosis surrogates or other non-invasive tests (NITs) to assess disease state. Therefore, disease trajectory is best assessed indirectly, through the occurrence or absence of clinically meaningful outcomes, specifically LREs including death, transplantation, and episodes of hepatic decompensation.

In this context, the absence of LREs in surviving, non-transplanted patients is most consistent with clinical stability over the follow-up period. Although histological regression of fibrosis would represent objective evidence of disease reversal, such assessment was not possible in this long-term observational setting, and is itself subject to sampling variability.[20,21] Importantly, LREs are among the strongest predictors of outcome in cirrhosis and are arguably more relevant to patient prognosis than changes in fibrosis stage alone.[22,23]

Although there is an increase in liver-related mortality in the cell-treated patients compared with control patients, the difference is not significant, and we speculate that this may reflect survivor bias in patients otherwise unsuitable for transplantation, whereby the most common cause of mortality would be liver-related outcomes.

Progressive immune dysfunction and heightened systemic inflammation are key drivers of acute decompensation in patients with stable cirrhosis, a state known as cirrhosis-associated immune dysfunction (CAID).[24,25] Elevated TNF-α levels have been linked to increased risk of liver decompensation, including hepatic encephalopathy[26]; however, more recent reports have failed to confirm this association.[27] The β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI) study was conducted almost exclusively in hepatitis C virus (HCV) cohorts; therefore, it may have limited generalizability and may also represent a distinct HCV-related immunophenotype.[28] In preclinical models, IL-4 signaling exerts context-dependent bidirectional effects on liver fibrosis, likely influenced by host microenvironment.[29] Importantly, IL-4-mediated activation of resident Kupffer cells can drive the alternative activation polarization program in macrophages,[29] downstream JAK3-STAT6 activation,[30] and subsequent fibrosis resolution.[31] This mechanism may underlie aspects of the present findings, particularly given the reciprocal changes observed in TNF-α expression. Although we caution against overinterpretation due to low patient numbers, our data suggest that stabilization of predominantly proinflammatory

cytokines, spanning both innate and adaptive immune pathways, correlates with improved survival during LTFU. Adaptive immune pathways are also evident in our analysis, which shows that increases in IL-2 were associated with poorer survival. Our observation of IL-7 modulation post-treatment is consistent with literature in which IL-7 has been associated with immunoreconstitution.[32,33] This could be important in this patient population, where CAID often leads to immunoparesis and an inability to respond to pathogens.[34] Therefore, one could speculate that the observed benefits likely derive from restoration of inflammatory equilibrium, supporting hepatic metabolic reserve and regenerative capacity. Consistent with this, a greater proportion of non-survivors exhibited declining circulating albumin levels, indicative of impaired hepatocyte regeneration and consequent loss of synthetic function.[35] Further studies aiming to characterize the immunological landscape of these patients and its relationship with functional markers of liver function will accompany future clinical phases of development of macrophage cell therapy in this patient population.[36]

Taken together, both phases of the MATCH01 study and the LTFU extension provide supportive evidence for the safety and potential efficacy of macrophage therapy in cirrhosis. Sustained improvements in liver function and clinical outcomes, coupled with the therapy's favorable safety and tolerability profile, support further clinical evaluation of this approach in patients with end-stage liver disease, where endogenous recovery is limited and pharmacological development has proven challenging. Across both phase 1 and phase 2 of the study, procedure-related adverse events associated with apheresis for MDM generation and subsequent re-infusion of the macrophage product were minimal, with excellent overall tolerability. Importantly, there were no signals suggestive of systemic inflammatory syndrome (SIRS) or macrophage activation syndrome (MAS) following cell infusion.[10,11]

Although macrophage therapy holds the promise of expanding therapeutic options for patients with advanced liver disease, future studies should define the mechanisms by which macrophages promote liver regeneration and fibrosis regression in humans, identify patient subgroups most likely to benefit, and validate long-term safety and efficacy in larger and adequately powered cohorts. Assessment of scalability and cost-effectiveness will be critical to ensure broad clinical adoption. Finally, in a related clinical study, the retained post-thaw potency of cryopreserved AAMs supports the potential for macrophages as an off-the-shelf therapy.[37]

In conclusion, long-term outcomes of the MATCH01 trial indicate the therapeutic potential of macrophage therapy in cirrhosis. By offering durable clinical benefits and a robust safety profile, this innovative approach represents a significant step forward in regenerative medicine.

Limitations of the study

MATCH01 was not originally designed, or adequately powered, to demonstrate the long-term clinical benefit of macrophage therapy. Consequently, this may have resulted in an underestimation of some observed effects, as attrition in the control group may have disproportionately influenced event rates when comparing across study arms. The relatively small sample size also limits the precision of the estimated effects. Given the small number of participants in the original trial and the progressive attrition rate, we would urge caution in over-extrapolating outcomes that the study was not powered to assess at the outset of the trial design. As noted above, the LTFU extension was also limited by incomplete data capture, variable reporting accuracy, and potential temporal bias, as patients reverted to routine care, often with asynchronous clinic visits or imaging schedules, compared with the rigorous timelines of clinical trials. Nevertheless, this reflects real-world practice and provides reassurance that no excess mortality or increased incidence of HCC was observed, particularly in the macrophage-treated group. It is also important to recognize inherent limitations of the original trial design, particularly the lack of supportive NITs such as spleen stiffness measurement as a surrogate marker of clinically significant portal hypertension (CSPH), which was not well validated or widely adopted at the time of trial initiation in 2016. The lack of liver tissue limits conclusions regarding changes in liver tissue architecture in response to macrophage therapy. There are, however, several considerations in this regard. First, liver biopsy performed for fibrosis assessment itself represents a proxy for predicting clinical outcomes such as LREs. It is increasingly recognized that biopsy, although traditionally considered the "gold standard," is sub-optimal,[38] and LREs can occur in patients without classical histological features of established cirrhosis.[39] Furthermore, liver biopsy carries procedural risk, especially in patients with CSPH. Histological assessment of fibrosis is also limited by sampling error and inter-observer variability, which has contributed to regulators seeking "reasonably likely surrogate endpoints" (RLSEs) for use in clinical trials.[40] Finally, the study was performed in an almost entirely White population, and the limited generalizability of these findings to more diverse populations should be acknowledged.

RESOURCE AVAILABILITY

Lead contact

Requests for further information should be directed to Stuart J. Forbes (stuart.forbes@ed.ac.uk).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Data reported in this paper are available from the lead contact (S.J.F.) upon reasonable request, although restrictions may apply due to patient privacy and the General Data Protection Regulation. This paper does not report original code. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: P.N.B., A.M.K., A.G., J.A.F., and S.J.F.; methodology: P.N.B., A.M.K., A.G., J.A.F., and S.J.F.; investigation: P.N.B., N.J.L., J.F.D., A.E., A.D., and J.A.F.; formal analysis: P.N.B., A.M.K., L.C., A.G., J.A.F., and S.J.F.; data curation: P.N.B., N.J.L., J.F.D., A.E., A.D., and J.A.F.; resources: A.G. and M.L.T.; writing – original draft: P.N.B., A.M.K., J.A.F, and S.J.F.; writing – review & editing: P.N.B., A.M.K., L.C., A.G., J.A.F., and S.J.F.; supervision: S.J.F.; project administration: S.J.F.

DECLARATION OF INTERESTS

P.N.B. reports consultancy or advisory board honoraria from Novo Nordisk, Madrigal, Boehringer Ingelheim, and Resolution Therapeutics, as well as educational support from Novo Nordisk and Takeda. A.M.K. is a consultant for Resolution Therapeutics. J.F.D. has received research grants and lecture honoraria from Merck Sharp & Dohme, AbbVie, and Gilead. L.C. is an employee and scientific co-founder of Resolution Therapeutics. J.A.F. serves as a consultant or advisory board member for Medicxi, Kynos Therapeutics, Resolution Therapeutics, Gyre Therapeutics, Ipsen, River 2 Renal Corp., Stimuliver, Guidepoint, and ICON plc; has received speaker fees from HistoIndex, Resolution Therapeutics, and the International Society for Continuing Professional Development (SICLEO); and receives research grant funding from GlaxoSmithKline and Genentech. S.J.F. is a founder of and adviser to Resolution Therapeutics and an adviser to Cytotheryx.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
CD163 (GHI/61)	Biolegend	333605; RRID:AB_1134005
CD169 (7-239)	Miltenyi Biotec	130-126-368; RRID:AB_2889466
CD206 (FITC 15-2)	Biolegend	321103; RRID:AB_571904
Biological samples		
Human blood samples	MATCH01 patients	N/A
Chemicals, peptides, and recombinant proteins		
Alburex (human serum albumin)	CSL Behring	43649
CliniMACS CD14 Reagent	Miltenyi Biotec	200-070-121
Human M-CSF GMP protein	R&D Systems	216-GMP
TexMACS GMP Medium	Miltenyi Biotec	170-076-307
Critical commercial assays		
V-PLEX Human Biomarker 54-Plex	Meso Scale Discovery	K15248G
Software and algorithms		
R (v 4.4.2)	R Core Team	https://www.r-project.org/
Cmprsk R package (v 2.2-12)	Fine and Gray[41]	https://CRAN.R-project.org/package=cmprsk
Corrplot R package (v 0.95)	Wei and Simko	https://github.com/taiyun/corrplot
Emmeans R package (v 1.11.1)	Lenth and Piaskowski	https://rvlenth.github.io/emmeans/
Hmisc R package (v 5.2-3)	Harrell	https://hbiostat.org/r/hmisc/
Lme4 R package (v 1.1-37)	Bates et al.[42]	https://github.com/lme4/lme4/
lmerTest R package (v 3.1-3)	Kuznetsova et al.[43]	https://github.com/runehaubo/lmerTestR
MASS R package (v 7.3-65)	Venables and Ripley[44]	https://cran.r-project.org/package=MASS
survival R package (v 3.8-3)	Therneau and Grambsch[45]	https://github.com/therneau/survival
survminer R package (v 0.5.0)	Kassambara	https://github.com/kassambara/survminer
STRING database (v 12.0)	Szklarczyk et al.[46]	https://string-db.org/
BioRender	BioRender	https://www.biorender.com/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The MATCH01 phase 1 trial evaluated the safety and feasibility of autologous monocyte-derived macrophage therapy in adults with compensated cirrhosis (MELD score 10 to 16),[10] while phase 2 evaluated its efficacy versus standard care in adults with MELD 10 to 17.[11,47] All surviving patients from MATCH01 (phase 1: $n = 9$; phase 2: $n = 24$ control, $n = 26$ macrophage treatment) gave informed consent for the LTFU study, with trial organizers tracking patient progress for an additional 3 years (i.e., total 4 years or 1,461 days post-randomization); we used all available data from patients who died during the phase 2 trial ($n = 2$ control group) (Figure S4). Initially, 3 cell infusions were planned in phase 2, however, this was streamlined to a single infusion of up to 1×10^9 cells[47]; no significant differences were observed between triple- and single-infused patients.[11] We therefore merged all cell-treated patients as a single cohort for LTFU analysis. Patient baseline characteristics were reported previously.[11] All patients considered for transplantation were referred to a single tertiary centre for evaluation, per international criteria (Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh).

Data collection followed a pragmatic, real-world approach, aligned with current clinical standards of care and conducted by the patients' treating physicians at their regional liver units. Assessments included liver function testing and monitoring of key clinical outcomes such as decompensation events, hospitalisations, hepatocellular carcinoma (HCC) surveillance, and liver transplantation. Patients were reviewed at six-month intervals in accordance with international best practice, during which these routine assessments were conducted.[48–50] Data were collated by research nurses and subsequently validated by an independent verifier. Liver-related events were defined by a physician to include conditions such as spontaneous variceal haemorrhage, ascites and hepatic encephalopathy.

The MATCH long-term follow-up study sponsor was the Academic and Clinical Central Office for Research and Development (ACCORD) (Sponsor number AC22134) which is a partnership between University of Edinburgh and NHS Lothian. The study underwent appropriate ethics committee review (Rec Number; 22/WS/0175) and was funded by the Medical Research Council (MRC) (Funding Reference No. MR/M007588/1)

METHOD DETAILS

Trial endpoints and outcomes

The MATCH01 phase 2 primary endpoint was the difference in baseline to day 90 change in MELD score (ΔMELD) between treatment and control groups (ΔΔMELD), using the original pre-2016 MELD score. This MELD formula is based on serum creatinine, bilirubin and international normalized ratio (INR):

$$MELD\ (\text{original, Pre-2016}) = 0.957 \times \ln(\text{creatinine, } \mu\text{mol / L}) + 0.378 \times \ln(\text{bilirubin, } \mu\text{mol / L}) + 1.12 \times \ln(\text{INR}) + 0.643.$$

The United Kingdom End-stage Liver Disease (UKELD) score was also calculated to indicate when patients might reach the theoretical threshold for liver transplantation, a key clinical decision point.[51] The UKELD formula is similar to MELD but also includes serum sodium:

$$UKELD = 5.395 \times \ln(\text{INR}) + 1.485 \times (\text{creatinine, } \mu\text{mol / L}) + 3.13 \times \ln(\text{bilirubin, } \mu\text{mol / L}) - 81.565 \times \ln(\text{sodium, mmol / L}) + 435.$$

Secondary outcomes included unplanned hospitalizations, decompensation events or hepatocellular carcinoma (HCC), liver transplantation, and death. HCC were diagnosed as part of regional multidisciplinary teams specialising in hepatobiliary medicine and oncology. Diagnosis was made on the basis of accepting radiological findings of HCC (using MRI or CT triple-phase contrast-enhanced scanning) i.e. arterial phase hyperenhancement with venous/delayed phase washout (LI-RADS criteria) as per international and EASL practice recommendations.[52]

Serum cytokine analysis

Serum cytokines were analysed as previously described in the MATCH phase 1 safety study.[10] Briefly, analysis used a V-PLEX Human Biomarker 54-Plex kit on a MESO Quickplex SQ 120 (Meso Scale Discovery), according to the manufacturers' instructions. Cytokine measurements were taken from cell-treated patients in the MATCH phase 2 RCT at baseline, and 7, 28 and 90 days after treatment; measurements were taken at 28 days and 90 days in control patients. Day 7 measurements were not available for control group patients due to a divergence in the follow-up schema. A complete list of cytokines is provided in Table S4. Percentage differences from post-treatment timepoints were computed and categorised as:

- "increase", if the difference was >=10% higher than baseline;
- "decrease", if the difference was >=10% lower than baseline;
- "unchanged", otherwise.

Proportions of each category were calculated, stratifying patients based on survival status at the end of the LTFU period. Fisher's exact test was used to test for significantly different proportions, for each cytokine and each timepoint.

To cluster cytokine expression patterns in cell-treated patients, for each cytokine, the difference between surviving patients and deceased patients was calculated for each category "increase", "decrease" and "unchanged", for each timepoint, to generate a vector of 9 differences. Pairwise Pearson correlations and associated significance values for cytokine measurements were computed with the Hmisc (v5.2-3) R package. The correlation matrix was visualised with the corrplot (v0.95) R package. Hierarchical clustering of the difference matrix was computed in R using Ward's method.

Albumin measurements from 90 and 360 days after treatment were categorised similarly to cytokine measurements as above, treating any increase or decrease relative to baseline as "increase" or "decrease" due to granularity of reported measurements. Measurements were similarly stratified based on patient survival status following the LTFU period. Fisher's exact test was used to test for differences in proportions of each category between day 90 and day 360.

Additional protein-protein interaction analysis was carried out using the online STRING database (v 12.0).[46]

Macrophage manufacture and characterization

Monocyte-derived macrophages were manufactured using good manufacturing practice (GMP)-compliant processes as described previously.[53] Briefly, steady-state leukapheresis was collected from each patient at the Scottish National Blood Transfusion Service (SNBTS) apheresis center in the Royal Infirmary of Edinburgh. Monocytes were isolated using a CliniMACS Prodigy cell processor with CliniMACS CD14 Reagent (both Miltenyi Biotec). $CD14^+$ cells were cultured in gas-permeable bags (MACS GMP cell differentiation bag 500; Miltenyi) in TexMACS GMP (phenol red-free) medium supplemented with 100 ng ml^{-1} GMP-grade macrophage colony-stimulating factor (M-CSF) (R&D systems). Macrophages were harvested after 7 days and prepared for injection supplemented with 0.5% human serum albumin (Alburex, CSL Behring).

Cell surface expression of leukocyte markers in freshly isolated and day 7 matured cells was assessed by flow cytometry, as described previously.[7,10,11,53] Briefly, cells were incubated with specific antibodies, for markers including those associated with

tissue repair and inflammation resolution, namely CD206 (FITC 15-2; Biolegend), CD163 (GHI/61; Biolegend) and CD169 (7-239; Miltenyi). Macrophage quality was assessed via retention of high levels of these markers. Marker fold changes in Figure 5 were computed as the ratio of minimum fluorescent intensity at day 7 to day 0.

QUANTIFICATION AND STATISTICAL ANALYSIS

Outcomes were analyzed on a time-to-event basis, comparing treatment groups. Kaplan-Meier estimators were used for survival analysis, with the composite endpoint of death or transplant. Hazard ratios and statistical significance were estimated using Cox proportional hazards regression. Survival analysis and proportional hazards regression models were computed using the survival R package (v3.8-3),[45] with additional visualization via survminer (v0.5.0). The proportional hazards assumption was evaluated using Schoenfeld residuals, with a loess-smoothed curve plotted against time for each covariate to visually assess potential departures from proportionality.

Cumulative incidence functions (CIF) were used for analysis of mortality with transplant as a competing risk, and for analysis of HCC, with mortality and transplant as a composite competing risk, and with mortality as sole competing risk. CIFs used the Fine-Gray sub-distribution hazard model and Gray's test (χ^2).[41] Recurrent event modelling of hospitalizations used a negative binomial regression model. We computed restricted mean survival time (RMST) and restricted mean time lost (RMTL) by treatment group, with truncation timepoint set to 1,461 days. Competing risks regression modelling and RMST analysis was performed using the cmprsk R package (v2.2-12).[41] RMST was calculated from the area under the cumulative incidence curve for the event of interest, accounting for competing risks, such that in this context it reflects the subdistribution of the event of interest. Confidence intervals and significance values for RMST analysis were computed via bootstrap resampling of patients within each group, with 1,000 bootstrap replicates.

ΔMELD and ΔUKELD trajectories were modelled using a linear mixed effects (LME) model, testing for interaction of treatment and time from randomization, with patient ID as a random effect to control for matched measurements. Post-transplant MELD and UKELD data were removed from MATCH phase 2 data before modelling, as applicable. We recorded no transplants in MATCH phase 1 data; therefore, all available MELD and UKELD data was used. LME models were implemented using the lme4 (v.1.1-37)[42] and lmerTest (v.3.1-3)[43] R packages and fit using the restricted maximum likelihood (REML) method. T-tests for LME models used Satterthwaite's method. Estimated marginal means for assessing differences at specified timepoints (365, 730, 1095 and 1460 days) with pairwise contrasts were computed using the emmeans R package (v.1.11.1).

Recurrent event modelling for hospitalizations used a negative binomial regression model, implemented using the MASS R package (v7.3-65)[44]; additional testing for overdispersion motivated the use of the negative binomial regression model over a Poisson model, which would have underestimated variability, given the data.

Macrophage quality, phenotyping and dosing data were tested for normality via Shapiro-Wilk test; all except CD169 were sufficiently normally distributed. Data were compared between survivors and non-survivors using t-tests (Mann-Whitney test for CD169).

Two-sided p-values <= 0.05 were considered to indicate statistical significance throughout.

ADDITIONAL RESOURCES

The MATCH01 clinical trial is registered with ISRCTN registration number: ISRCTN10368050.