Cell based therapy in inflammatory liver disease - the MERLIN trial

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Mesenchymal stromal cells (MSC)

- Heterogeneous population of precursor cells
- Multiple sources of MSC

Potential applications of MSC in liver disease

- Cirrhosis
- Metabolic liver disease
- Alcoholic hepatitis
  - Autoimmune liver disease
  - Graft rejection
- Replace with functioning hepatocytes
- Stimulate hepatocytes and oval cells

MSC have a pleiotropy of action on the immune system

Alfaifi M et al. J Hep 2018
MERLIN programme: MEsenchymal stromal cells to Reduce Liver INflammation

Pintail
Orbsen
UoB
NHSBT
UNIPD

Efficacy
Mechanism of action
CD362+ MSC
Clinical trial
Immune-mediated liver disease

Autoimmune hepatitis
- Anti-SMA, anti-LKM-1
- SLA/LP, F-actin, anti-LC-1
- Plasma cells
- Interface hepatitis
- Elevated IgG
- Corticosteroid response

Primary sclerosing cholangitis
- ANCA
- Cholangitis in the young
- Radiological evidence of bile duct injury
- Periductal fibrosis
- Cholestasis
- Concurrent colitis

Primary biliary cholangitis
- Antimitochondrial antibodies
- Specific ANA (gp210, sp100)
- Histological small bile duct destruction
- Elevated IgM
- Sicca complex

Webb GJ et al. Annu Rev Pathol Mech Dis 2018
Primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) share the same immune-pathogenesis

- Multifactorial-genetic and environmental factors
- Complex disease pathogenesis

Webb GJ et al. Annu Rev Pathol Mech Dis 2018
Studies

• Experimental

- In vivo studies in 3 murine models: UC-MSC effect on hepatic inflammatory activity (ALT and CD45) and T cell infiltration
- In vitro studies: UC-MSC effect on T cell proliferation and activation using tissues from patients with PSC

• Clinical trial

- Safety and efficacy of UC-MSC in patients with PSC and AIH
In vivo models of inflammatory liver injury

- **Ovalbumin (Ova)- Bil mouse model**: Transgenic mouse model of immune-mediated hepatobiliary injury

- **C57BL/6 mice**: Carbon-tetrachloride-induced liver injury (CCL$_4$)

- **Chronic Mdr2 KO/FVB mouse model**: Model of sclerosing cholangitis
Human CD362+ UC-MSC reduce inflammation in 3 mouse models of inflammatory liver injury

**Mdr2⁻/⁻**

**Ova-Bil**

**CCl₄**

Data from V Wigneswara & M Alfaifi

UC- Umbilical cord
US: Unselected MSC

ALT

Hepatic CD45

No MSC
MSC
Infusion of CD362+ UC-MSC reduce hepatic CD3+, CD4+ & CD8+ T cell infiltration in the chronic model of sclerosing cholangitis

* Data from V Vigneswara

* *p < 0.05
Infusion of CD362+ UC-MSC induces CD4⁺CD25⁺Foxp3⁺ Tregs

Data from V Vigneswara

* $p < 0.05$

** $(p=0.0021)$

** $(p=0.0044)$
In-vitro assessment of efficacy of UC-MSC in patients with PSC

- Effect of UC-MSC on CD4\(^+\) and CD8\(^+\) T cell proliferation and activation

T cell proliferation and activation
UC-MSC suppress peripheral blood CD4⁺ and CD8⁺ T cell proliferation from patients with PSC

Key
Stim: stimulated PBMC only

**** p≤0.0001
UC-MSC reduce peripheral blood CD4+ T cell activation

* p ≤ 0.05
UC-MSC suppress Intrahepatic CD4$^+$ and CD8$^+$ T cell proliferation from patients with PSC
UC-MSC reduce intrahepatic CD4⁺ T cell activation from patients with PSC
Summary of MSC actions

CD362+ UC-MSC

- Induction of Tregs
- Reduction of CD3, CD4, CD8
- Reduction of proliferation and activation of CD4, CD8
- Reduction of hepatic inflammation
- Reduction of biliary epithelial cell inflammation and death

Parameters:
- TNFα
- IFNγ
MSC clinical trials in liver disease

- MSC therapy has been used in a number of clinical studies to treat liver disease (n=300)
- Found to be safe
- Variability in efficacy
- Most studies have short follow-ups so long-term efficacy data is lacking
Primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH)

PSC

- Prevalence 16.2 per 100,000 inhabitants
- Affects young patients
- No licensed effective therapies

AIH

- Prevalence 16-18 cases per 100,000 inhabitants
- 10-20% patients are treatment intolerant or unresponsive
- Therapies limited by side-effects & limited 2nd line options
Unmet needs of patients with PSC and AIH

Patients with PSC

- Mean transplant-free survival = 14.5 years

Patients with AIH

- Higher mortality risk for AIH patients compared to matched general population

Weismüller & Trivedi et al. Gastro 2017

Groenbark et al. J Hep 2014
Bucket trial concept

Common mechanistic and clinical primary end point
Primary Outcome measures

• Safety and Feasibility

• Disease end-point
  ➢ Change in serum ALP (PSC) and ALT (AIH) from baseline

• Mechanistic end-point
  ➢ Increase in circulating Tregs
**Trial design**

**Inclusion criteria**

**Patients with PSC**
Serum ALP ≥ 1.5 ULN at screening visit

**Patients with AIH**
Patients refractory to treatment
Serum ALT ≥ 1.5 ULN at screening visit

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**STAGE 1**
Determine: Safety at a higher dose

**STAGE 2**
Determine: EFFICACY and safety

1.0 $\times 10^6$ cells/kg  
n=3  
Safe  

2.5 $\times 10^6$ cells/kg  
n=3  
Safe  

Stage 2

Safety: Assessed by dose limiting toxicity (DLT) and adverse events

Chief Investigator: Prof Gideon Hirschfield  
Co-CI: Prof Philip Newsome
Patient pathway in the trial

Screening Visit 1
Pre-treatment Visit 2
MSC infusion
Treatment Visit 3
Registration

SD -28 | SD -7 | SD 0

Primary efficacy outcome measures: Change in ALP (PSC)/ALT (AIH) from baseline

Secondary efficacy outcome measures: Long term safety f/u

Significant clinical events and serious adverse events will be captured

SD = study day
Clinical trial progress

- Ethical and regulatory approval (MHRA) obtained - April 2017
- Substantial amendment to MHRA submitted - April 2018
- Aim to recruit 19 patients per cohort
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