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Commentary

Macrophage therapy and liver regeneration: Results and perspectives

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ABSTRACT

The recent results of the study evaluating the impact of macrophage transplantation in cirrhosis with the aim of improving liver function open up a number of prospects. Although negative, fewer deaths were observed, as well as a favourable cytokine profile. This is in line with other results obtained in liver disease, notably through signalling and regeneration studies on human liver tissue. For the future, a number of questions need to be answered if we are to make progress in this fascinating field.

We find the subject of liver regeneration in chronic liver disease extremely fascinating, as is the concept of administering macrophages for pro-regenerative purposes [1,2]. Regarding this subject, we have been able to demonstrate in humans the link between macrophages and liver regeneration processes including proliferation of hepatocytes and, very interestingly, proliferation of liver progenitor cells [3,4]. As mentioned in this journal a few years ago, we also believe that liver progenitor cells give rise to intermediate hepatocytes and create fully functional adjacent hepatocytes that may be beneficial for the regeneration of the human liver in chronic diseases [5]. This occurs in a context of a lack of therapeutic possibilities for advanced cirrhosis and the need for an alternative or bridge to liver transplantation due to the lack of organs [1,6].

The group of Stuart J. Forbes (Centre for Regenerative Medicine, University of Edinburgh) has been working on this subject for many years and on developing ex vivo matured monocyte-derived macrophages [7]. Indeed, macrophages, previously considered harmful because they are associated with the inflammatory process, are now also recognised as guarantors of effective innate immunity, capable of effectively eliminating apoptotic/necrotic cells and modulating the local fibrous tissue microenvironment [1,7]. In a recent manuscript published in Nature Medicine, the researchers Paul N. Brennan, Stuart J. Forbes and colleagues describe an interventional randomized, controlled trial on the efficacy of autologous monocyte-derived macrophage therapy in compensated cirrhosis [8]. Although the primary endpoint - the difference in MELD score at 3 months from baseline - did not differ between the two groups, the authors showed that no deaths occurred in the treated arm compared with four deaths in the placebo arm, and highlighted an increase in circulating levels of interleukin-15 (IL-15) and a decrease in interleukin-1beta (IL-1β) in the treated arm, both attributed as beneficial [8].

We have three comments to share on this subject.

Firstly, we also carried out a randomized controlled trial in Geneva in which patients with decompensated cirrhosis due to alcohol-related liver disease (ALD) either received or did not receive G-CSF injections followed by autologous bone marrow mononuclear cell transplantation into the hepatic artery [9]. As in the authors' study [8], this treatment made no significant difference in terms of the number of patients achieving a reduction in MELD score [9]. However, we also noted a positive message concerning mortality with only two deaths in the treated arm compared with four deaths in the control arm [9].

Secondly, the researchers mention that a limitation of their study was the lack of pre- and post-treatment liver biopsies [8]. We collected this type of sample in our study [9] and analysed both the markers of regeneration on histology and the major pathways using RNA sequencing. These results were the subject of a second publication [10]. We showed a regenerative stimulus at the molecular level and, on histology, an expansion of liver macrophages in the treated group [10]. We interpreted this stimulus as favourable but too weak in the context of advanced liver disease [6,10]. However, this stimulus is important to note in view of the authors' results [8].

Thirdly, we think it is important to discuss the perspectives, and we feel it is necessary to obtain the opinion of specialists on the subject. In view of these weak but potentially encouraging results, what options should be favoured from now on? It might be interesting to aim for a longer-term, more sustained treatment (several infusions), to agree on precise secondary endpoints or biomarkers, and, lastly, probably to identify subtypes of liver disease that might respond to different stimuli, rather than bringing together what are sometimes very different diseases in the same trial. Indeed, recent studies differ in terms of inclusion criteria: decompensated cirrhosis due to alcohol-related steatohepatitis [9,10], or compensated cirrhosis mainly due to ALD, metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic hepatitis C [11] or mainly due to ALD and MASLD for the most recent [8]. Depending on their specific pathophysiology, an increase in IL-15 or other macrophage-related cytokine, for example, may be more effective in certain conditions, deleterious in others, or beneficial at certain precise stages of severity [6,12–14].

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In this context, continuing to gain a better understanding of the mechanisms involved in liver regeneration [5,15], communication between cells and their microenvironment [1,16,17] and inter-organ communications [14,18–20] will help to develop clinical strategies in the field of liver failure.

CRediT authorship contribution statement

Nicolas Lanthier: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Laurent Spahr:** Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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