Comparative study of intravenous and topical administration of mesenchymal stem cells in experimental colitis

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Abstract

Adult marrow-derived mesenchymal stem cells (MSCs) have anti-inflammatory properties in patients with Inflammatory Bowel Disease (IBD), but systemic delivery is associated with safety concerns. Whether topical delivery of MSCs would provide similar efficacy to systemic administration is unknown. To compare topically-delivered MSCs to systemic administration, and non-MSC therapy, in animal model of colitis. Trinitrobenzenesulfonic acid (TNBS) colitis was induced in Wistar rats. Topical MSCs were compared to intravenous MSCs, adalimumab, infliximab and control in this model. Serial measurements of clinical criteria were used (i.e., weight, stool characteristics), and serum interleukin 6 (IL-6) and TNF measurements and macroscopic and microscopic scores were used to evaluate treatment efficacy. Topical and intravenous stem cell treatments, significantly prevented weight loss in TNBS mice on day 3 of colitis. There was greater evidence of a difference mainly on the third day (p<0.001). IV or PR stem cells also reduced serum IL-6 and TNF levels to similar levels to those of anti-TNF treated animals. In the intestinal tract, stem-cell treatment ameliorated the microscopic and macroscopic damage caused by TNBS. Rectal-delivered stem cells produced similar results to IV-delivered cells. This study demonstrates that rectal stem cells can treat colitis in an animal model to a similar extent to IV stem cells and systemic anti-TNF therapies. The mechanisms of this effect warrants further study.

Introduction

Inflammatory bowel diseases have pathophysiologies based on genetic inheritance associated with environmental factors related either to the intestinal lumen or not, and produce an exacerbated inflammatory response, resulting in intestinal or extraintestinal clinical manifestations [1-4]. In recent years, experimental models have significantly contributed to the understanding of these diseases, allowing the development of drugs with high specificity that act directly on target inflammatory mediators, such as Tumor Necrosis Factor alpha (TNF-alpha) and adhesion molecules, among others. This advancement has enabled treatment providers to change the natural history of these diseases, increasing the quality of life of affected patients and decreasing hospitalization and surgical intervention rates [5]. Although these drugs have modified the treatment scenario, primary drug failure due to loss of response has been observed over the years [6]. Primary failure has corresponded to more than 40% of cases [7], and serial clinical studies indicate a primary failure rate of 10 to 20%. During one year, this loss of response may vary between 23 to 43% of cases [6]. Genetic factors, disease duration, smoking and even the production of antidrug antibodies have been associated with primary failure [6,8].

Conversely, recent studies indicate the possibility of using an immune path (cell therapy) different from drug therapy in patients who are intolerant to conventional drug treatments or when such treatments fail [9].

Cell therapy could represent the optimization of intestinal factors produced by mesenchymal stem cells, which have demonstrated the capacity to inhibit TNF-alpha and Interleukin 6 (IL-6) by regulating the incorrectly exacerbated immune response and inducing intestinal homeostasis, producing an important clinical response for healing the colonic mucosa in both experimental models and humans [9-11]. One of the limiting factors of this treatment is associated with opportunistic infections and uncontrolled cell development, which lead to neoplasms [12,13]. In addition to these data, these cells have the capacity to migrate to the lesion site, even when applied far from the lesion [1,14].

Such lines of evidence have encouraged the studies regarding the topical application of these cells in the colon, which has potential as a new drug strategy and may decrease the side effects of this therapy [1].

Objectives

This study aims to assess the applicability and the results of mesenchymal stem cell implantation in animals submitted to...
Discussions

The present study is unprecedented, as applied in Wistar animals, and compares the effect of mesenchymal stem cells applied via enema and intravenous with other already known therapies, such as anti-TNFs [18].
Infliximab (p<0.05), which might be due to the fact that Adalimumab tended to take longer to restore their weight than those treated with Adalimumab (p<0.001). Clinically, animals treated with Adalimumab was more evident in animals treated with Infliximab followed by those treated with saline (blood test). However, these differences were observed between the anti-TNF agents (p<0.995 and p<0.994, respectively), and both were similarly effective for healing the mucosa.

Macroscopically and microscopically, all treated animals exhibited better scores, compared with the sick groups (Figures 4 and 5). No differences were observed between the anti-TNF agents (p<0.995 and p<0.994, respectively), and both were similarly effective for healing the mucosa.

Histological and macroscopic recoveries were also observed with stem cells, with no difference between the two treatments (p<0.995 and p<0.604, respectively). Thus, we observed that, even when applied via enema, the stem cells had a therapeutic effect.

Previous studies have indicated that the cell response is initially interpreted by the migration of these cells to the target location and by the differentiation of these cells in target tissues. This fact explains why, when administering the treatment in the colon via enema, the cell response was sufficient [1]. Hez et al. demonstrated the capacity of mesenchymal cells to inhibit both IL6 and TNF-alpha and to induce histological repair, with similar results compared with those demonstrated here [1].

Physiologically, these effects appear to be directly associated with paracrine signals, which favor the migration of stem cells to the lesion site, regardless of its location. Another hypothesis is based on cell-to-cell contact combined with the multiplication of cells similar to their matrix, with the modulation properties of the inflammatory immune response and the release of cytokine inhibitors and reactive oxygen species (NO) acting with scanning effects on the inflammatory cascade [20]. Other studies also report a preventive action of cell therapy in the presence of TNBS damage [7].

Recently, Stavely et col. showed that in animal models of colitis (guinea pig bone marrow MSCs) the mesenchymal stem cell is able to immunomodulate the inflammatory response due to its capacity of effective penetration and leukocyte infiltration into the mucosa and myenteric plexus and sources secreted TGF-β1 [21,22]. Thus, the combination of these factors have demonstrated themselves to be one of the mechanisms via which experimental colitis caused by TNBS can be attenuated [22].

Experiments with enema of mesenchymal stem cells have been applied in guinea-pigs demonstrating the effectiveness of these cells in the treatment of neuropathy and plexitis. As well as MSCs derived from adipose tissue [23,24].

Knowing studies in guinea-pigs seem to more effectively simulate Inflammatory Disease as it happens in humans when compared to experimental models in Wistar rats. However, both studies can reinforce new pathways to the applicability of these cells by enema [25].

We used the cell therapy only when the damage had already been...
established, but recent studies have demonstrated that these cells could prevent tissue damage [26-29].

Conclusion

This study suggests new methods for treating inflammatory bowel disease in relation to the use of topical and intravenous applications of stem cells. Although we have had better results via intravenous, we believe that in the future stem cell applications via enema can present an alternative with less side effects. The assessment of clinical parameters, microscopic and macroscopic scores and chemical mediators of inflammation (including IL-6 and TNF-alpha) all support these conclusions. Additional studies should be conducted to obtain further evidence of these associations.

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