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The use of multi-potent Mesenchymal Stromal Cells for control of inflammatory Bowel disease

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Abstract:

Despite availability of a large variety of anti-inflammatory agents with broad spectrum of reactivity against autoimmune and non-specific inflammation, disease activity cannot always be adequately controlled and some approved conventional agents can result in severe, potentially life-threatening complications. Safer and more effective control of inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis remain unmet need. In recent years, a new cell-mediated procedure induced by multi-potent mesenchymal stromal cells (MSCs) is emerging as a potential safer and more effective modality for control of inflammatory reaction in IBD with additional potential benefit - repair of existing tissue damage. Autologous MSCs can be obtained from the bone marrow by aspiration, from the fat tissue by liposuction, or using unrelated MSCs derived from placenta & cord tissue. The number of MSCs can be easily expanded in culture using no growth factors. MSCs attracted spontaneously to sites of inflammation and tissue damage and can turn off any inflammation or anti-self-reactivity resulting from an autoimmune disease. Furthermore, MSCs can be differentiated into cells resembling nearly every tissue and as such may also repair existing tissue damage and prevent fibrosis. Systemic or even intra-thecal treatment of MSCs is safe based on our experience in more than 500 patients treated for different indications, mostly neuroin-flammatory and neurodegenerative disorders and a few with IBD. The exquisite anti-inflammatory effects inducible by MSCs are best documented by control of otherwise resistant graft-vs-host disease following allogeneic stem cell transplantation, considered the most potent, not infrequently fatal, inflammatory reaction. Based on our cumulative experience, using MSCs is likely to become the treatment of choice for patients with resistant IBD, especially Chron's disease, and later on also for patients at an early stage of their disease in order to avoid deterioration of damage to the gastro-intestinal tract, while avoiding hazardous non-specific anti-inflammatory agents.

Keywords: Inflammatory bowel disease, Mesenchymal stem cells, Systematic review and meta-analysis, adverse effects, efficacy

Introduction:

Inflammatory bowel disease (IBD) which comprises of Ulcerative Colitis (UC) and Crohn's Disease (CD), is presumed to result from an inappropriate response of the host's immune system to intestinal microbes. The existing management strategies for IBD therefore target inflammation and include immunosuppressive therapy with corticosteroids, azathioprine, 6 mercaptopurine (6-MP), monoclonal antibodies against cytokine tumors necrosis factor alpha (infliximab, adalimumab, certolizumab pegol and golimumab), the recently approved integrin inhibitor Vedolizumab (anti-α4β7 Integrin), and surgery . A recent study of monotherapy versus combination therapy in UC patients showed induction of clinical remission (defined as a total Mayo score of 2 points or less, with no individual sub score exceeding 1 point, without the use of corticosteroids) in 23.7% by azathioprine, in 22.1% by infliximab and in only 39.7% of patients by combination therapy at 16 weeks .

Thus, approximately 60% of UC patients failed to achieve clinical remission at 16 weeks even with combination therapy. Similarly, the SONIC study (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) for CD patients, showed induction of clinical remission in 30% of patients by azathioprine, in 44.4% by infliximab and in 56.8% of patients by combination therapy at 26 weeks.

Methods:

We followed the standard Cochrane guidelines and the PRISMA statement for

performing and reporting systematic review.Search strategy: A systematic review of English and non- English articles was performed using PubMed (since inception to March 2015) and EMBASE (since inception to November 2014). The search was performed independently by the authors (MD, KM and JL), and by an information library specialist (Larry Prokop).

Study selection: Studies were selected based on the following inclusion criteria: (i) Human studies (ii) Included patients with IBD (iii) MSCs were used for treatment of IBD (iii) No preparatory regimen for immunosuppression that is whole body irradiation or myeloablation (iv) Efficacy and adverse events were reported (v) The study was published as peer reviewed paper, letter or abstract.

Data extraction: Two independent reviewers (K.M & M.D) extracted data from the selected studies using standardized data extraction forms. These forms included: a) Author b) Journal c) Year of publication d) Country where study was performed e) Type of study f) Sample size g) Number of CD cases and UC cases h) Number of healthy controls (if any) i) Type and source of stem cells j) Primary outcome k) Efficacy outcome and m) Adverse events.

Statistical analysis: The primary outcomes of this analysis were proportion of patients with healed fistula after local injection of MSCs as defined by the study investigators and proportion of patients with induction of remission after systemic infusion of MSCs. Freeman-Turkey transformation was used to calculate pooled proportions under the fixed and random effects model.

Results:

Search results: The initial search strategy yielded 4828 abstracts for review, of which 36 were selected for detailed review and 12 met the inclusion criteria .Twenty-three studies were excluded for being non-human studies or using myeloablative preparatory regimen or radiation. A study by Herreross et al. was excluded; as it was a randomized, single blind trial of ASCs vs. fibrin glue vs. ASCs plus fibrin glue in 200 patients with cryptoglandular perianal fistulas and did not include IBD patients. We first report the efficacy and safety of stem cells for perianal CD which involved local application of stem cells and then report the efficacy and safety of stem cells for luminal IBD separately as that involved systemic infusion of stem cells.

Efficacy of SCT for Peri-anal CD (Local therapy): Garcia-Olmo et al., in 2003, were the first investigators to report a case of successful healing of perianal fistula in a CD patient (who previously failed multiple immunosuppressive therapies) by local injection of autologous adipose derived stem cells (ASCs) . The same group later conducted a phase I trial of local injections of autologous ASCs in five CD patients who had rectovaginal, perianal and/or enterocutaneous fistulas. The study demonstrated complete closure in three out of four rectovaginal or perianal fistula (75%) and three out of four enterocutaneous fistulas (75%) at eight weeks post treatment

Discussion:

Our systematic review and meta-analysis suggests that SCT has good therapeutic potential with low risk of adverse events for

IBD patients, particularly for those who have perianal disease and are treated with local therapy. The major advantage of mesenchymal SCT is that it does not require preparatory regimens involving high dose chemotherapy and/or radiation like bone marrow/hematopoietic stem cell transplant. As a result, it is associated with less adverse events and procedure related mortality. MSCs have regenerative and immunomodulatory properties which lead to decrease of aggravation and mending of influenced intestinal tissue.

Conclusion:

MSCs are emerging as an alternative treatment for refractory IBD. Although, MSCs appear safe and potentially effective in initial studies, more studies in preclinical animal models and human studies that incorporate randomized controlled design are needed. Recent basic science advances in biology of MSCs needs to be incorporated in clinical trials to improve the efficacy of MSCs.