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ORIGINAL ARTICLE

Long-Term Follow-Up of Crohn Disease Fistulas After Local Injections of Bone Marrow–Derived Mesenchymal Stem Cells

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Abstract

Objective: To assess the long-term outcome of patients treated with serial intrafistular injections of autologous bone marrow–derived mesenchymal stem cells (MSCs) for refractory Crohn fistulas in terms of safety and efficacy.

Patients and Methods: Starting from January 10, 2007, through June 30, 2014, clinical evaluation, calculation of the Crohn disease activity index (CDAI), therapeutic management, and documentation of adverse events in 8 of the 10 patients (5 men; median age, 37 years) who had been injected locally with MSCs were prospectively recorded for 72 months. Cumulative probabilities of fistula recurrence and medical or surgical treatment were estimated using a Kaplan-Meier method, whereas differences among the pre- and post-MSC CDAI values were calculated with the Mann-Whitney *U* test.

Results: Following disease remission observed after 12 months from MSC treatment ($P<.001$), the mean CDAI score increased significantly during the subsequent 2 years ($P=.007$), and was then followed by a gradual decrease, with the patients achieving remission again ($P=.02$) at the end of the 5-year follow-up. The probability of fistula relapse-free survival was 88% at 1 year, 50% at 2 years, and 37% during the following 4 years, and the cumulative probabilities of surgery- and medical-free survival were 100% and 88% at 1 year, 75% and 25% at 2, 3, and 4 years, and 63% and 25% at 5 and 6 years, respectively. No adverse events were recorded.

Conclusion: Locally injected MSCs constitute a safe therapy that rescues refractory patients and regains responsiveness to drugs previously proved ineffective.

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Fistulizing Crohn disease (CD)[1] is a challenging condition for both the clinicians involved in its management and the patients who have a poor quality of life.[2] Before the introduction of biological agents as first-line therapy, approximately half of these patients experienced fistula recurrence after the first treatment with anal surgery and 40% had to eventually undergo a proctectomy.[3] The advent of anti–tumor necrosis factor-α therapy, mainly based on the use of infliximab, has allowed the achievement of complete healing rates of 55% and clinical response rates of up to 68%, at least in the short term.[4] Moreover, combined medical and surgical strategy has recently been shown to perform better than surgery or medical therapy alone in attempting to relieve incapacitating symptoms such as pain, discharge, and fecal incontinence while favoring fistula healing and avoiding definitive stoma.[5] However, the benefit in terms of sustained fistula closure has proved to be limited, with a relapse rate of 16% at 1 year, 31% at 3 years, and 40% at 5 years,[6] with an increased risk of opportunistic infections[7] and malignant neoplasms[8] due to immunosuppressive treatment. These high recurrence rates and adverse events, therefore, highlight the need for a better therapeutic approach in terms of both long-lasting efficacy and safety.

After the pioneering work of Garcia-Olmo and coworkers[9-11] on the use of adipose tissue–derived mesenchymal stem cells (MSCs), we carried out a phase I-II study aimed at investigating the feasibility, safety, and efficacy of local

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injections of autologous bone marrow–derived MSCs in patients with refractory fistulizing CD, which yielded promising results.[12] Specifically, up to 70% of the patients achieved complete closure of fistula tracks, as assessed by a combination of clinical, surgical, and imaging evaluations, whereas the remaining 30% benefited from an improvement, with a parallel significant reduction in both the Crohn disease activity index (CDAI) and the perianal disease activity index (PDAI), without the appearance of any adverse effects during the 12-month follow-up period.[12] Our results were subsequently confirmed in a phase II clinical trial in which 43 patients with fistulizing CD were treated with local injections of autologous adipose tissue–derived MSCs and monitored for the same follow-up period.[13] Here, we aimed to evaluate the outcome of the patients described in our previous publication[12] along further 5 years of follow-up to clarify the long-term safety and efficacy of this therapeutic strategy in terms of fistula relapse, as well as medication- and surgery-free remission.

PATIENTS AND METHODS

Study Population and Protocol

Starting from January 10, 2007, through June 30, 2014, 10 patients with CD who had undergone serial intrafistular injections of autologous bone marrow–derived MSCs (median, 4; range, 2-5; scheduled at 4-week intervals) as compassionate use for patients with refractory disease or inability to undergo standard therapies[12] were prospectively enrolled in this study. The study parameters, including careful clinical and perianal examination, routine laboratory tests, and calculation of the CDAI,[14] were assessed 12 months after the last cellular injection and then yearly for a further 5 years to diagnose and record possible adverse events and to monitor clinical efficacy. A cutoff CDAI value of 150 points or less was considered indicative of disease remission.[14] Surgical examination and magnetic resonance imaging (MRI) were also carried out yearly, and in the event of fistula relapse, MRI was evaluated according to the categories and score proposed by van Assche et al.[15] For patients unable to return for follow-up visits and those who moved to other centers, phone and e-mail contacts were established to collect data on symptom recurrence, interval medications, surgery, hospitalization, and laboratory tests. The PDAI[16] score was obtained only in those patients who returned for physician evaluation. A cutoff PDAI score of more than 4 was established as indicative of active fistula disease.[16] In this regard, a fistula track was considered "closed" when it no longer drained despite gentle finger compression; *fistula remission* was defined as the absence of any draining fistula opening, and *response* was defined as a reduction of 50% or more in the number of draining fistulas.

The primary outcomes were to evaluate the sustainability of efficacy and the occurrence of any adverse effects related to the locally delivered stem cell therapy. More specifically, *efficacy* was defined as the achievement of a CDAI score of less than 150 and a PDAI score of less than 4, whereas safety evaluation included analyses of systemic tolerance, adverse events (eg, a noxious reaction), and serious adverse events (ie, a life-threatening condition requiring hospitalization or resulting in disability or death), as specified in the *Medical Dictionary for Regulatory Activities* System Organ Class categorization. Serious adverse events were reviewed as they occurred, whereas cumulative adverse events were recorded every 6 months by R.C. In addition, unexpected events were monitored, in particular any opportunistic infections or the appearance of signs or symptoms of cancer. Secondary outcomes included fistula relapse-free survival, and both *medical- and surgery-free remission*, defined as the time lapse from the start of the MSC treatment to the recurrence of symptomatic disease requiring medical or surgical treatment therapy. Specifically, only the introduction (or reintroduction) of a biological agent and/or immunosuppressant drug was regarded as an event because pharmacological treatment, including aminosalicylates, antibiotics, and azathioprine, was allowed at stable dosage during both the cellular treatment and the first 12 months of the study, whereas biological therapy had been interrupted on enrollment.

Ethical Considerations

The study was conducted according to the Good Clinical Practice guidelines, the International Conference on Harmonisation guidelines, and the ethical principles set out in the Declaration of Helsinki. The protocol was approved by the institutional ethics committee, and each patient gave written informed consent.

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