



## Stem Cell Transplantation for Treatment of Crohn's Fistulae

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### Editorial

Up to 20% of patients with Crohn's disease (CD) may have perianal fistula disease, which is frequently associated with perianal collections [1]. Classically, surgery has played an important role, by the placement of drains or setons creation of ostomies, and in severe cases, even proctectomy [2]. However, in recent years, medical treatment with or without the temporary placement of drains, has taken a leading role. Immunosuppressants such as azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine have proven beneficial in many patients. In more complicated cases where these drugs are ineffective, biological treatments based on monoclonal antibodies have been shown to have some success for the induction and maintenance of remission of perianal fistula disease and associated proctitis [3]. Still, the percentage of patients who do not respond or do so only partially remain significant. Furthermore, the existence of serious complications associated with treatment should not be overlooked [4].

It is as a result of these inadequacies in current treatment strategies that cell therapy has arisen as a complementary option [5]. The promising results published in recent years, both with autologous and in allogeneic cells, highlight a need for greater understanding of the basic principles of this new route, and for clarification of the current state of the topic.

Adult stem cells can be obtained using much simpler methods, and have no restrictions or ethical considerations. Furthermore, because of their autologous origin, they are not immuno reactive. Early studies using adult stem cells have focused on mesenchymal stem cells (MSCs). These can be found in the stroma of virtually every organ, for example, in subcutaneous adipose tissue and bone marrow. Being fibroblastoid cells, they are the precursors of all types of non-haematopoietic connective tissues (bone, fat, cartilage, etc.). MSCs are generally obtained by selection through adherence to tissue culture plastic, as they are able to adhere and grow in conditions where other cell types do not usually proliferate [6].

MSCs have a high capacity for proliferation and differentiation. Furthermore, under certain experimental conditions, they have displayed the ability to differentiate into non-connective cell lineages, such as neuronal and endothelial. Finally, as a particularly interesting property for the use at hand, they are capable, both in vitro and in vivo, of inhibiting immune response. This ability to immuno regulate includes inhibition of the activation of T-, B-, and NK-cells, the maturation of dendritic cells, as well as protecting against inflammatory and/or autoimmune pathologies, including transplant rejection [7].

The precise mechanism of the therapeutic action of MSCs is not fully understood, but is likely to reflect their inherent characteristics, in particular their differentiation potential [8]. MSCs have the ability to migrate to the site of a lesion or inflammatory process, stimulate the proliferation and differentiation of resident stem cells through the secretion of growth factors, remodel the matrix, and exert an immunomodulatory and anti-inflammatory effect. Together, these properties aid help the healing of tissues [9]. It has also been demonstrated that MSCs can induce an increase in epithelialisation and angiogenesis through a process of differentiation and paracrine interaction with skin cells [10].

The first experience with stem cells in the treatment of anal fistulae was reported by Garcia-Olmo et al. [10]. Several studies have since been published, the majority of which are from Spanish groups. The MSCs used have mainly originated from adipose tissue, with only two studies using bone marrow MSCs. In these latter cases, both allogeneic and autologous cells have been used. In all studies, administration was intralesional, with fibrin glue often used [12].

Today, any questions as to the feasibility and safety of such treatment seem to have been

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resolved, at least within the range of doses used. A retrospective study evaluating whether MSC treatment has any influence on fertility, course of pregnancy, birth weight, or physical status was recently published [13]. Five patients with fistula associated with Crohn's disease treated with ASCs, and who indicated their intention to have children after completion of treatment, were tracked. Fertility and pregnancy course were not found to be affected by this therapy. Furthermore, no treatment-related malformations in newborns were observed. Therefore, it was concluded that in the patients analysed in the study, local injection of ASCs was not associated with adverse effects on the ability to conceive, pregnancy course, or the newborn's condition.

In the published literature there are differences in cure rate depending on the follow-up, but in general it is estimated to be between 50 and 70%.

Ciccocioppo et al. [12] evaluated the long term safety and efficacy of the use of bone-marrow-derived MSCs. In their study, 8 patients were followed prospectively for 72 months. These patients were part of a phase I/II trial previously conducted, in which a cure rate of 70% per year was reported, with improvement observed in the remaining 30%. Patients received serialised injections of MSCs (4 on average) at intervals of 4 weeks. Secondary endpoints were the time patients remained without fistula and the time they were free of medical or surgical treatment. The Crohn's Disease Activity Index (CDAI) increased over the first two years, followed by a gradual decline in the third year, and stabilisation at the end of follow-up at figures similar to those of the first year. The probability of remaining without fistula was 88% for the first year, 50% at two years, and 37% over the next four years. The probability of patients being free from surgery was 100% for the first year, 75% for years 2 to 4, and 63% at years 5 and 6. Finally, the probability of patients being free from medical treatment was 88% for the first year, 25% at years 2 to 4, and 25% at years 5 and 6. No adverse effects related to treatment in these follow-up periods were recorded. The authors conclude that the fact that the activity indices increase again in the second year might suggest that this therapy is not curative, but that it does improve the remission rate in patients with refractory disease. Moreover, almost all patients required the reintroduction of biological or immunosuppressive therapy after the second year [12].

The safety and feasibility of local eASC administration has been demonstrated in Phase I/IIa study in which Cx601 was injected at doses of 20 million cells with an additional dose of 40 million cells in case of incomplete fistula closure at Week 12, without apparent safety signals. This trial (in which only one tract was treated) showed that a percentage of patients not responding to 20 million cells could be healed with an additional higher dose of 40 million cells 12 weeks after the first dose [14].

Recently we published the results of a phase III, randomised, placebo, double-blind, multicentre, and international clinical trial employing Cx601, a preparation of allogeneic ASCs. Cx601 was statistically superior to placebo in achieving the combined response (clinical and imaging) of complex perianal fistulas in Crohn's disease patients whose response to previous treatment, including anti-TNFs, had been inadequate. The follow up was 24 week [15].

There is no doubt that a new avenue has opened for the treatment of Crohn's disease patients suffering from fistulae refractory to conventional therapy. Since the first description of the treatment,

interest in this therapy has grown, so that in addition to the 11 studies published to date, at the time we write this chapter, there are more than a dozen clinical trials in recruitment or in the results publication phase. While the safety of ASC therapy seems to have been well established, the optimal dosage, route of administration (intravenous versus intralesional), administration technique (alone or together with fibrin glue), among other matters, are yet to be adequately determined. However, these should be investigated and resolved in the coming years.

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