Stem Cell Application in Fistula Disease

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The Rationale for Cell Therapy to Treat Anal Fistula

Cell therapy has emerged as a new tool to improve wound healing in a number of settings. In mammals, wound healing begins when a number of different cell types that arrive at the wound area in a step known as the "cellular phase." There are pathological situations in which this cell supply is deficient and wound healing may be delayed or not achieved, this is the case of anal fistula.

Stem cell transplantation provides a way of increasing the number of cells locally in this critical phase with the aim of restoring normal wound healing. In the case of anal fistula, wound healing is a critical item. Even treatment of a simple fistula is complicated as the surgeon will need to access the sphincter and, in doing so, may compromise its integrity leading to fecal incontinence. Limited surgical treatment often results in high recurrence whereas extensive surgical treatment may cause fecal incontinence [1]. Surgical flaps and other surgical techniques have the handicap of healing in a septic environment. Recurrence is almost always due to occult sepsis that has initially escaped surgical detection and has, thus, gone untreated. Recurrent fistulas pose a notoriously difficult surgical challenge and multiple failed operations are the rule rather than the exception in these patients. Such a state of affairs complicates matters as the perianal scarring and distortion that inevitably accompanies multiple surgical attempts at cure makes the preoperative assessment more and more complicated, which further complicates identification of unsuspected areas of sepsis. The inevitable result is that these individuals are progressively more difficult to treat with both patient and surgeon becoming ever more exasperated [2]. Moreover, continuous suppuration in the anal region in unhealed or recurrent fistulas leaves the patient at risk of acute infection with abscess formation, which will require urgent surgical drainage. Importantly, chronic fistulas could lead to tumor development (mainly anal epithelial carcinoma) due to the irritation caused by constant suppuration.

In the case of anal fistula associated to Crohn's disease, recent improvements in medical treatment (e.g., infliximab and adalimumab) add to expert surgical management, have decreased the need for complicated surgery [3–5], but many patients are not cured completely and fecal incontinence remains a problem [6–8].

In this scenario, cell therapy is envisaged as an effective alternative to surgery. The promising preclinical and clinical data that we will review below suggest that cell therapy could represent a major advance in the clinical management of this difficult problem.

Choosing Type of Stem Cells

Stem cells (SCs) are generally defined by being undifferentiated, with a capacity for long-term self-renewal and the potential to undergo multilineage differentiation from a single cell. Some authors include in vivo production of functional tissues as another defining characteristic [9]. They can undergo facultative symmetric or asymmetric division in which they simultaneously perpetuate themselves and give rise to a second daughter cell programmed to differentiate. Different SC types have been considered for preclinical and clinical applications in digestive tract diseases, unfortunately, in the clinical practise an optimal SC type has not been found [10].

To the date, only mesenchymal stem cells (MSCs) have been used to treat anal fistula. Nevertheless the place of extraction of this kind of cells can be different. MSCs were initially described as a bone marrow-derived mononuclear cell population that, when cultured ex vivo, adhered to plastic

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with a fibroblast-like morphology. MSCs exist in the bone marrow and other tissues such as fat. The International Society for Cellular Therapy (ISCT) established three minimal criteria that MSCs must fulfill in vitro: adherence to plastic, specific surface antigen expression pattern (CD73+ CD90+ CD105+ CD34− CD45− CD11b− CD14–CD19− CD79a− HLA-DR−) and differentiation potential (osteogenic, chondrogenic, and adipogenic lineages) (Revised by García-Gómez et al. [11]).

MSCs have been reported to be immunoprivileged cells. Although the mechanisms underlying the immunosuppressive effects of MSCs have not been clearly defined, it seems that MSCs modulate the function of different cells involved in the immune response. The therapeutic potential of MSCs is currently being explored in a number of clinical trials. At present time only three Phase III clinical trials have been concluded for graft-versus-host disease (GVHD), Crohn's disease, and perianal fistula [11].

Since ex vivo-expanded MSCs have become a good option in a clinical setting, it is necessary to pay attention to the safety of cellular therapies. To achieve this aim, optimized culture conditions and isolation protocols are being developed. Additionally, precise genetic stability studies have been developed to ensure the quality and biosafety of MSCs in clinical practice. Overall, we are seeing how the evolution of stem cell research in the last decade is converting the MSCs into a new medical product that can be useful to treat anal fistula.

Fat appears as a great source of stem cells; liposuction can achieve large quantities of stem cells, and then can be harvested with minimal adverse effects.

Mechanism of Action of Stem Cell to Improve Healing

Somehow, we can say that the basis for fistula recurrence is a defect in the wound healing process. There is much scientific and clinical interest in the potential of MSCs to stimulate wound repair. Mesenchymal stem cell-based therapies represent a new treatment for preventing morbidity and disability associated with chronic wounds, an unresolved clinical problem that has shown little improvement over the past decades [12]. Healing of a cutaneous wound requires a well-orchestrated integration of complex, biological, and molecular events and such processes may be impaired in many chronic diseases [13]. Functional characteristics of MSCs, like their ability to migrate to the site of injury [14] or inflammation and to stimulate proliferation and differentiation of resident progenitor cells through growth factor secretion and matrix remodeling, and their immunomodulatory and anti-inflammatory effects, may benefit wound healing.

Recent studies have demonstrated that treatment of cutaneous wounds with bone marrow MSCs accelerates wound healing kinetics and increases epithelialization and angiogenesis [15–17], suggesting that MSCs enhance wound repair by at least two different mechanisms: differentiation and paracrine interactions with specific cell types in the cutaneous wound [18]. Considered together, the MSC treatments for delayed wound healing are associated with dermal rebuilding in addition to remodeling, an increase in wound vascularity, and reduced fibrosis or scarring [19].

MSCs from fat injected in the site of inflammation recognize proinflammatory cytokines, like IFN-gamma, and consequently activate IDO enzyme. We showed that tryptophan breakdown products such as kynurenine and 3-hidroxyanthranilic acid (3-HAA) can inhibit lymphocyte proliferation. These data suggest that IDO exerts its effect through the local accumulation of tryptophan metabolites, creating a microenvironment able to suppress the proliferation of activated lymphocytes including T cells and NK cells [20]. Once the proliferation of reactive lymphocytes is controlled, the pro-inflammatory mediators are reduced (TNF-a, IL6, IL12, IL1-b, etc.), the anti-inflammatory mediators are increased (IL-10) and the inflamed environment is restored. In summary, the proposed mechanism of action of this kind of cells for the treatment of anal fistula is primarily based on anti-proliferative and anti-inflammatory effects. According to this mechanism, eASCs deliver immunomodulatory signals that suppress inflammatory molecules and reactive lymphocyte proliferation, diminishing the inflammatory environment allowing the fistula tract to heal (Fig. 18.1) [20].

The application of MSC therapy in human wounds show excellent results from studies in the last years [15, 21, 22] and hence, in the treatment of complex perianal fistulas as we describe below.

Routes of Stem Cells Administration to Treat Anal Fistula

In clinical practise, most of experiences have been directed to treat anal fistula related with Crohn's disease. In this context two routes of administration have been tried: intravenous (systemic) and intralesional.

Intravenous injection has been used by the Group sponsored by Osiris Therapeutics that, to the date, do not provide publications of the results (*A Phase III, Multicenter, Placebo-controlled, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of PROCHYMAL[tm] Intravenous Infusion for the Induction of Remission in Subjects Experiencing Treatment-refractory Moderate-to-severe Crohn's Disease*. Responsible Party: Osiris Therapeutics. ClinicalTrials.gov Identifier: NCT00482092; http://www.clinicaltrials.gov/). They are using intravenous infusion of suspension of allogenic

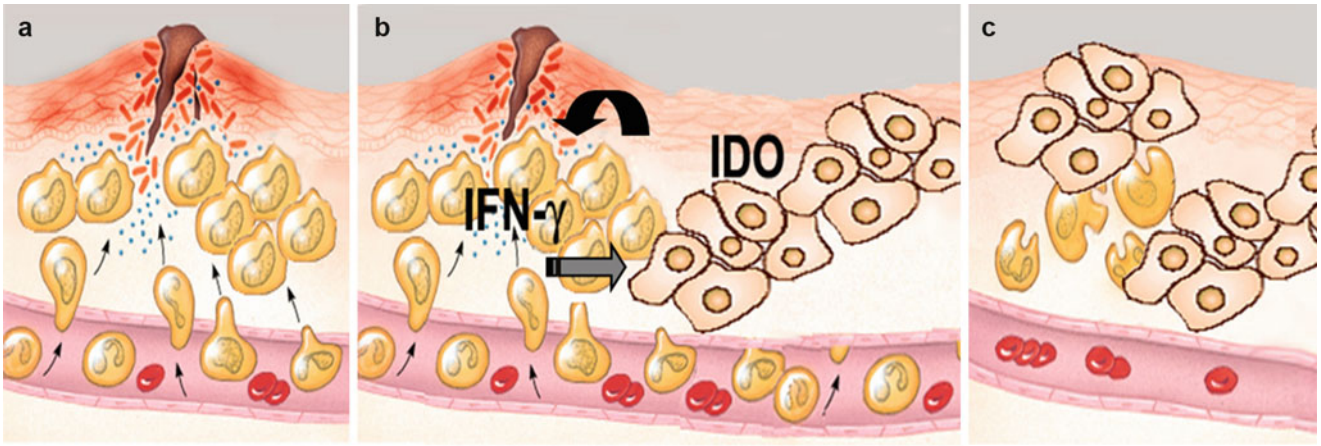

Fig. 18.1 Scheme of the mechanism of action of allogeneic eASCs in the tract of the anal fistula: anti-inflammatory and antiproliferative effect in an inflamed local environment (Courtesy of María Pascual). (**a**) MSCs from fat injected in the site of inflammation recognize proinflammatory cytokines. (**b**) IDO enzyme exerts its effect suppressing the proliferation of activated lymphocytes including T cells and NK cells. Once the proliferation of reactive lymphocytes is controlled, the proinflammatory mediators are reduced (TNF-a, IL6, IL12, IL1-b, etc.). (**c**) The anti-inflammatory mediators are increased (IL-10) and the inflamed environment is restored

adult human MSCs, total of 1,200 million (high dose) or 600 million (low dose) cells infused in four visits over 2 weeks. These adult human stem cells are manufactured from healthy, volunteer donors, extensively tested, and are stored to be available as needed. According with the Osiris information, human and animal studies have shown that the cells do not require any donor–recipient matching. The cells may have both immunosuppressive and healing benefits in Crohn's disease. The cells naturally migrate specifically to sites of inflammation, so their effects are believed to be local and self-limiting rather than systemic. Currently, they are enrolling subjects to evaluate the ability of PROCHYMAL to induce remission in subjects with moderate-to-severe disease (Crohn's disease activity index—CDAI—of between 250 and 450, inclusive) who have failed or been intolerant of at least one drug in each of the steroid, immunosuppressant, and biologic classes (http://www.clinicaltrials.gov/). Although publications are not available is important to remark that this protocol is now running as a Phase III clinical trial (http://www.clinicaltrials.gov/).

The rest of the experiences using stem cells to treat fistulas have been designed using cells in intralesional way. One of them is using autologous MSCs from bone marrow [23] and the others from fat (autologous and allogenic) as we describe ahead (see Tables 18.1, 18.2, 18.3, and 18.4).

Cells from bone marrow are isolated after an aspiration and MSCs were expanded ex vivo to be used for to treat fistula [23]. Cells from fat are named adipose-derived stem cells (ASCs) and are a suspension of living adult stem cells of mesenchymal origin extracted from adipose tissue of subdermal origin obtained in a liposuction procedure (Fig. 18.2). Subdermal adipose tissue has a heterogeneous cell component comprising mast cells, endothelial cells, pericytes, fibroblasts, and the stem cells of interest with multilineage capacity (ASCs). The ASCs are isolated by digesting the adipose tissue with collagenase, followed by differential centrifugation and adherence to tissue culture plates with subsequent in vitro expansion [24]. The phenotype and the cell growth kinetic data demonstrate that the ex vivo expansion of ASCs does not alter their biological properties significantly as regards their proliferation capacity, morphological characteristics, and surface marker expression pattern and potency. The cell population present in the final product has therefore remained essentially unchanged throughout the whole expansion procedure [24].

Protocols of intra-fistula cell injections include the following steps: tract curettage, closure of internal opening, and cell injection. To be exact, after the initial experiences in 2002 [25, 26], the protocol described in 2009 [27] is currently followed by our Team and has 5–6 steps (Fig. 18.3):

1. Tract identification, with special emphasis on location of the internal opening.
2. Tract curettage with special emphasis on intersphincteric tracts.
3. Closure of the internal opening, if possible, with a Vicryl 2/0 (Ethicon) stitches.
4. Cell suspension and immediate use to prevent cells from settling.
5. Injection of cell suspension through a long fine needle (e.g., Abocatt 20; Terumo) into the tract walls, with half of the total cells being placed in the intersphincteric tracts and those adjacent to the internal opening and the other half being placed in the tract walls in the direction of the external opening. Injections were very superficial, no deeper than 2 mm.
6. In some cases we performed a sealing of the fistulous tract with fibrin adhesive.

Table 18.1 Published clinical experiences of stem cells treatments of anal fistula (Part 1)

Investigators	Year of publication	Trial code	Location	Condition	Study design	Cells source	Expanded	Cells number
García-Olmo et al. [25]	2003	NA	Spain	Recto-vaginal fistula in Crohn's disease	Case report	Autologous fat	Yes	1×10e7
García-Olmo et al. [26]	2005	Not registered	Spain	Enterocutaneous, recto-vaginal, perianal fistula in Crohn's disease	Phase I	Autologous fat	Yes	1–3×10e7 resuspended in fibrin glue
García-Olmo et al. [27]	2009	NCT0011 5466	Spain	Perianal fistula with or without Crohn's disease	Phase II	Autologous fat	Yes	Not specified
García-Olmo et al. [31]	2010	NA	Spain	Recto-vaginal fistula in Crohn's disease	Case report	Allogeneic fat	Yes	Not specified
Ciccocioppo et al. [23]	2011	NA	Italy	Enterocutaneous and complex perianal fistula in Crohn's disease	Case report	Autologous bone marrow	Yes	5×10e7
Cho et al. [32]	2012	NCT0099 2485	Korea	Perianal fistula in Crohn's disease	Phase I	Autologous fat	Yes	Not specified
Herreros et al. [28]	2012	NCT0047 5410	Spain	Complex perianal fistula without Crohn's disease	Phase III	Autologous fat	Yes	2×10e7 then 4×10e7 when no effect
Herreros et al. [28]	2012	NCT0102 0825	Spain	Complex perianal fistula without Crohn's disease	Observational	Autologous fat	Yes	2×10e7 then 4×10e7 when no effect
Guadalajara et al. [33]	2012	Not registered	Spain	Perianal fistula with or without Crohn's disease	Observational	Autologous fat	Yes	Not specified
de la Portilla et al. [34]	2012	NCT0137 2969	Spain	Perianal fistula in Crohn's disease	Phase I/II	Allogeneic fat	Yes	2×10e7 then 4×10e7 when no effect

It is important to remark that the technical items were showed as a key point, because after a Phase III clinical trial [27], we could observe objective evidence that the surgical expertise using cell therapy in anal fistula is a major item, i.e., our results in the Phase II study [27], the healing rate was of 70 %, whereas we achieved a healing rate of 83.3 % in the Phase III, although the baseline characteristics of the patients were similar in both [28].

Other techniques are described in uncompleted clinical trials, like successive injections in site without surgery.

The number of cells applied to the patients in the published studies is still low. The first step is to prove a safe profile of this treatment. This number is rising gradually, expecting that the success of the therapy is a matter of volume of cells.

Evidence Related to the Use of Stem Cells to Treat Anal Fistula

In order to analyze evidences about the safety and efficacy of stem cells in the treatment of anal fistulas, we have performed two different systematic reviews. The first one includes all published clinical data in Medline (keyword: fistula, stem cells) and the other one reviews all data available in ClinicalTrials.gov (A service of the U.S. National Institutes of Health (http://www.clinicaltrials.gov/)).

Systematic Review of Published Clinical Data (Tables 18.1 and 18.2)

We identify ten papers published that include data about clinical treatment of the anal fistula using stem cells. The first one was published in 2003 [25] and the last one recently, in 2012 [34]. Eight of them are from Spanish groups and the other two, one from Korea [32] and the other one from Italy [23]. Mostly are directed to treat anal fistula related with Crohn's disease. Only one study [23] treated fistulas using bone marrow as a cell source. The rest of the studies are using autologous or allogenic cells from fat. In all studies, cells were expanded with a wide range of doses (Table 18.1). Except the Italy study [23], procedures include the internal opening closure but in all cases the cell injections were intralesional. About 300 patients have been enrolled in this studies and the more important result is directed to assure that the safety profile of the stem cells are excellent: no serious adverse events related with cells were described. Regarding efficacy results show very different profiles, but we can say that about 40–60 % of patients achieve healing (Table 18.2).

Table 18.2 Published clinical experiences of stem cells treatments of anal fistula (part 2)

Investigator	Intervention model	Masking	Procedure	Enrolled	Number of treated patients	Healed	Follow up (months)	Recurrence	SAE[a]
García-Olmo et al. [25]	Single arm	Open label	Closure of IO. Without fibrin glue. Injection in site	1	1	1	3	0	0
García-Olmo et al. [26]	Single arm	Open label	Cells resuspended in fibrin glue. Injection in site	9	9	6	12	Not specified	0
García-Olmo et al. [27]	Two arms: fibrin glue, fibrin glue + ASCs	Open label	Closure of IO. Injection in site	50 (35 with Crohn's disease,	Fibrin glue: 25 Fibrin glue + ASCs: 24	Fibrin glue: 3 Fibrin glue + ASCs: 17	12	Fibrin glue: 0 Fibrin glue + ASCs: 2	4 (only one related to Fibrin glue, others not related)
García-Olmo et al. [31]	Single arm	Open label	Closure of IO. Without fibrin glue. Injection in site	1	1	1	36	1	0
Ciccocioppo et al. [23]	Single arm	Open label	Four injections in site	12	10	7	12	0	0
Cho et al. [32]	Single arm: dose escalation study	Open label	Closure of IO. Fibrin glue. Injection in site	10	9	3 of 9	15	0	0
Herreros et al. [28]	Three arms: fibrin glue, ASCs, fibrin glue + ASCs	Double blind (subject, Outcomes Assessor)	Closure of IO. Injection in site	214	ASCs: 64 Fibrin glue + ASCs: 60 Fibrin glue: 59	ASCs: 27 Fibrin glue + ASCs: 24 Fibrin glue: 23	6	ASCs: 0 Fibrin glue + ASCs: 4 Fibrin glue: 0	4 Unrelated to study treatment
Herreros et al. [28]	Three arms: fibrine, ASCs, fibrin glue + ASCs	Double blind (subject, Outcomes Assessor)	Closure of IO. Injection in site	135	Not specified	ASCs: 57 % Fibrin glue + ASCs: 52.4 %Fibrin glue: 37.3 %	12	Not specified	1 Unrelated to study treatment
Guadalajara et al. [33]	Two arms: fibrin glue, fibrin glue + ASCs	Open label	Closure of IO. Injection in site	34	Fibrin glue: 13 Fibrin glue + ASCs: 21	Fibrin glue: 3 Fibrin glue + ASCs: 10	38	Fibrin glue: 1 Fibrin glue + ASCs: 5	0
de la Portilla et al. [34]	Single arm	Open label	Closure of IO. Without fibrin glue. Injection in site	34	24	9	4	Not specified	2 Unrelated to study treatment

ASCs adult stem cells, *SAE* serious adverse events
[a]Requiring hospital admission longer than 24 h

Table 18.3 Ongoing clinical trials using stem cells for treatment of anal fistula (part 1)

Trial code	Condition	Sponsor	Investigator	Study start date	Location
NCT01157650	Enterocutaneous, recto-vaginal, perianal fistula in Crohn's disease	Clínica Universidad de Navarra, Universidad de Navarra	Prosper F	2010	Spain
NCT00999115	Recto-vaginal fistula in Crohn's disease	Instituto de Investigación Hospital Universitario la Paz	García-Olmo D	2009	Spain
NCT01314092	Complex perianal fistula without Crohn's disease	Anterogen Co., Ltd.	You CS	2011	Korea
NCT01586715	Extremely complex perianal fistula	Instituto de Investigación Hospital Universitario la Paz	García-Olmo D	2012	Spain
NCT01440699	Perianal fistula in Crohn's disease	Anterogen Co., Ltd.	Kim TI	2011	Korea
NCT01623453	Complex perianal fistula without Crohn's disease	Anterogen Co., Ltd.	Park KJ	2011	Korea
NCT01144962	Perianal fistula in Crohn's disease	Leiden University Medical Center	Hommes DW	2010	the Netherlands
NCT01011244	Perianal fistula in Crohn's disease	Anterogen Co., Ltd.	You CS	2010	Korea
NCT01548092	Recto-vaginal fistula in Crohn's disease	Instituto de investigación Hospital Universitario la Paz	Herreros MD	2011	Spain
NCT01584713	Enterocutaneous fistula with or without Crohn's disease	Instituto de Investigación Hospital Universitario la Paz	García-Arranz M	2011	Spain
NCT01314079	Perianal fistula in Crohn's disease	Anterogen Co., Ltd.	You CS	2011	Korea
NCT01541579	Perianal fistula in Crohn's disease	Tigenix	Not specified	2012	Europe, Israel
NCT00482092	Crohn's disease (reduction in number of draining fistulas)	Osiris Therapeutics	Custer L	2007	USA, Australia, Canada, New Zealand

Source: Clinicaltrials.gov (http://www.clinicaltrials.gov/)

Table 18.4 Ongoing clinical trials using stem cells for treatment of anal fistula (part 2)

Trial code	Cells source	Expanded	Cells number	Status	Phase	Intervention model	Masking	Estimated enrollment
NCT01157650	Autologous fat	Yes	Not specified	Recruiting	1, 2	Single arm	Open label	15
NCT00999115	Allogeneic fat	Yes	2×10e7, when no effect 4×10e7	Completed	1, 2	Single arm	Open label	10
NCT01314092	Autologous fat	Yes	1×10e7 or 2×10e7. Additional double dose when no effect	Recruiting	2	Two arms: low dose, high dose	Single blind (subject)	40
NCT01586715	Autologous fat	Yes	Not specified	Recruiting	2	Single arm	Open label	10
NCT01440699	Allogeneic fat	Yes	1×10e7 or 3×10e7	Recruiting	1	Single arm	Open label	6
NCT01623453	Autologous fat	Yes	1×10e7 or 2×10e7. Additional double dose when no effect	Active, not recruiting	2 (Follow-up)	Two arms: low dose, high dose	Single blind (subject)	40
NCT01144962	Allogeneic bone marrow	Yes	1×10e7, 3×10e7, 90×10e7	Recruiting	1, 2	Four arms: control group, ASCs	Double blind	21
NCT01011244	Autologous fat	Yes	Depending on the surface area of fistula	Completed	2	Single arm	Open label	40
NCT01548092	Autologous fat	No	Not specified	Recruiting	1, 2	Single arm	Open label	10
NCT01584713	Autologous fat	No	Not specified	Recruiting	1, 2	Single arm	Open label	10
NCT01314079	Autologous fat	Yes	Depending on the surface area of fistula	Ongoing, not recruiting	2 (Follow-up)	Single arm	Open label	40
NCT01541579	Allogeneic fat	Yes	12×10e7	Recruiting	3	Two arms: (ASCs, Placebo)	Double blind	208
NCT00482092	Allogeneic bone marrow	Yes	1,200 million or 600 million cells infused in four visits	Recruiting	3	Three arms: placebo, high dose and low dose	Double blind	270

ASCs adult stem cells
Source: Clinicaltrials.gov (http://www.clinicaltrials.gov/)

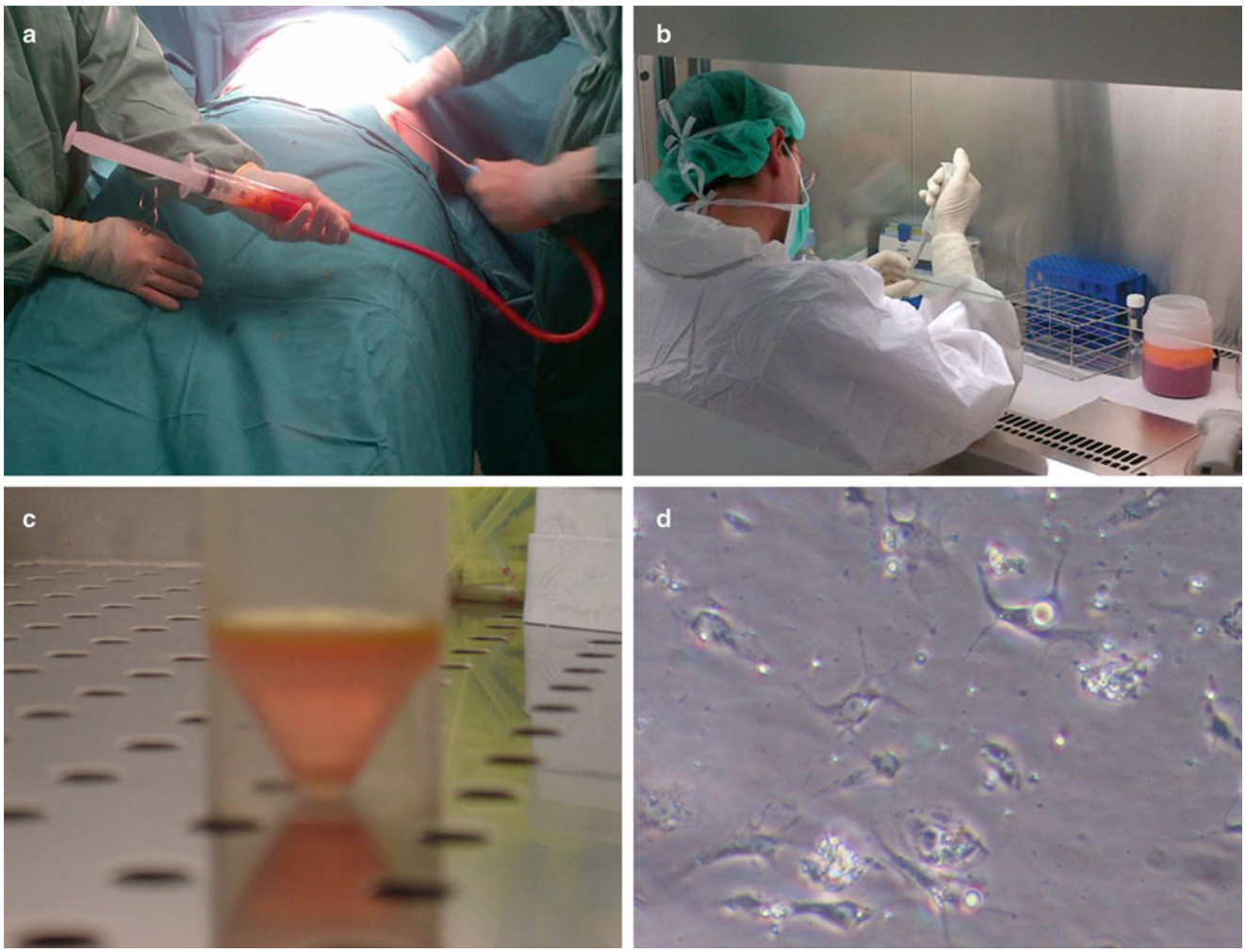

Fig. 18.2 Process of extraction of cells from fat (ASCs). (**a**) Liposuction with local anesthesia and little incision. (**b**) The ASCs are isolated by digesting the adipose tissue with collagenase, followed by differential centrifugation and adherence to tissue culture plates with subsequent in vitro expansion. (**c**) Stromal vascular fraction: subdermal adipose tissue has a heterogeneous cell component comprising mast cells, endothelial cells, pericytes, fibroblasts, and the stem cells of interest with multilineage capacity. (**d**) Microscope picture of ASCs before expansion. The phenotype and the cell growth kinetic data demonstrate that the ex vivo expansion of ASCs does not alter their biological properties significantly as regards their proliferation capacity, morphological characteristics, and surface marker expression pattern and potency. The cell population present in the final product has therefore remained essentially unchanged throughout the whole expansion procedure

Ongoing Clinical Trials (Tables 18.3 and 18.4)

To the date, 13 trials directed to treat anal fistula using stem cells were identified in Clinicaltrials.gov (http://www.clinicaltrials.gov/). Twelve of them are focused exclusively in Crohn's disease. Korea and Spain have registered five and the Netherlands one, all of them in Phase I or II. The other two clinical trials are multinational studies in Phase III. One of them is developing in Europe and Israel under Tygenix SL sponsorship. The other Phase III clinical trial is running in the USA, Australia, Canada, and New Zealand under Osiris Therapeutics sponsorship (Table 18.3).

Autologous or allogenic fat is the cells source in 11 studies and the two others use bone marrow as a cell source in an allogenic mode (Table 18.4). Two of these clinical trials have been completed (NCT00999115 and NCT01011244) but to the date data have not been published. The total estimated patient enrollments are 270 patients and the majority of results are expected by 2015.

From Present Experiences: A Look to the Future

Indeed, new approaches are therefore needed in the treatment of anal fistula due to outcomes are far from ideal given the problems of fecal incontinence in the case of aggressive surgery or recurrence in the case of less aggressive surgery.

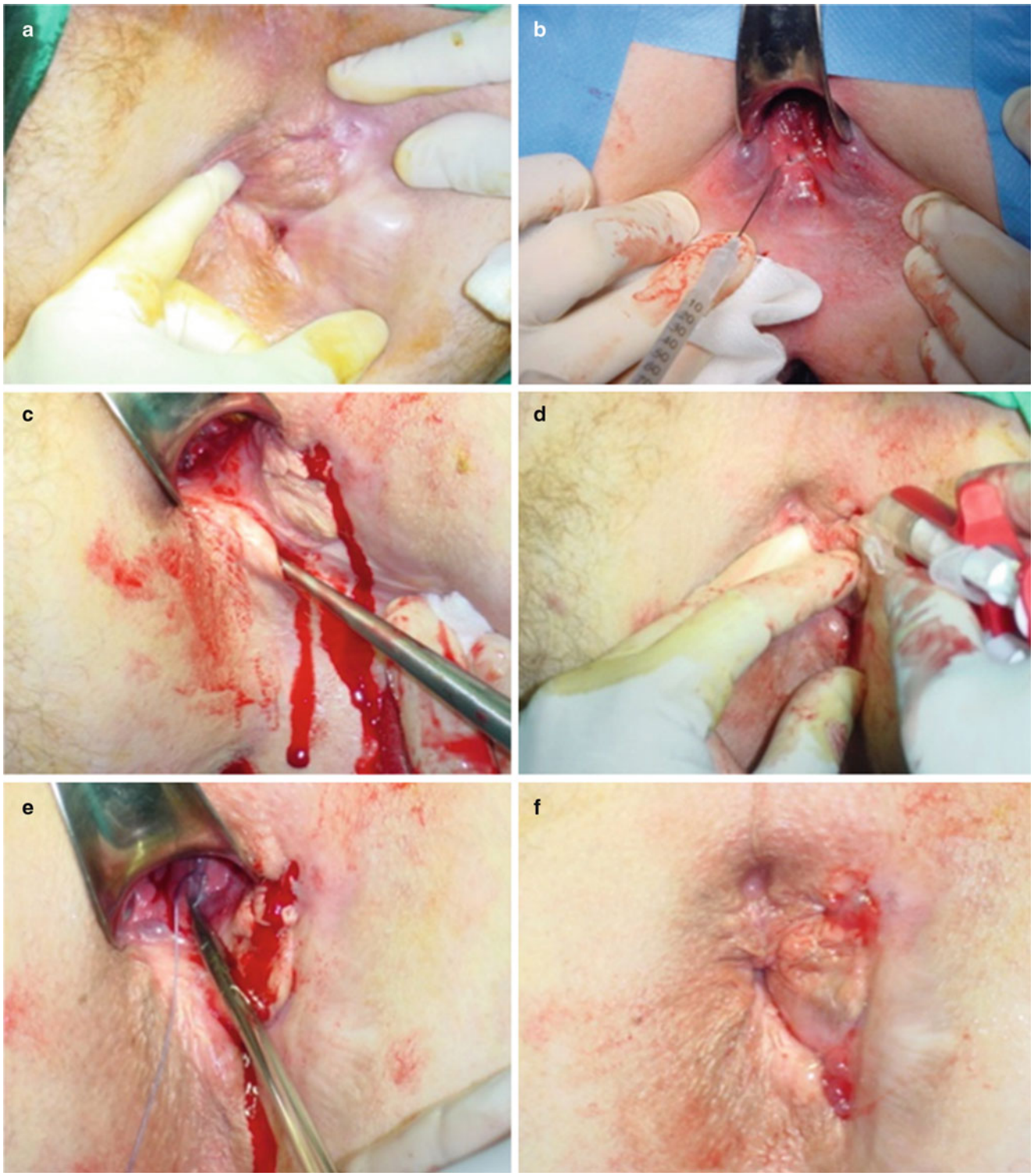

Fig. 18.3 Surgical protocol for intra-fistula cells injection. (**a**) Tract identification; (**b**) cells injection in internal opening; (**c**) curettage; (**d**) tract sealant; (**e**) internal opening closure; (**f**) final view

Stem cells appear to be a novel tool for the repair of damaged tissues. Their use exploits two coordinated biological effects, namely, immunoregulation and the local suppression of inflammation on the one hand and the proliferation and differentiation of cells on the other.

Randomized controlled studies using stem cells to treat anal fistula has been conducted, and all of them show an excellent safety profile. Nevertheless, the real efficacy is hard to assess. The outcome of the only Phase III clinical trial published [28] was negative in that the primary outcome

measure was not met, but there are certain indications, in line with the preceding studies, suggesting that the procedure can be effective in the right conditions. Furthermore, long-term results showed that the healing rate at 1 year was double for the use of ASCs with or without fibrin in comparison with fibrin glue alone. That's one of the reasons why further studies should be performed to better define the most beneficial scenario for stem cell therapy in patients with anal fistula.

Is this approach to treat complex anal fistula worth pursuing? Any decision will be influenced by the fact that surgery is the only accepted effective treatment for complex anal fistula. Despite healing rates above 60 %, surgery is associated with incontinence rates between 10 and 35 % and recurrence rates between 11 and 45 % [29, 30]. With cell therapy, there is no injury to the anal sphincter because tract resection is not required and repeated doses can be used to increase the chance of healing. In addition, adult stem cell therapy is not subject to the major ethical concerns. On the other hand, the cost of therapy with stem cells is difficult to ascertain at present. For our Phase II study [27], the cost of producing pharmaceutical grade cells (i.e., Good Manufacturing Practice (GMP) compliant) was in the range of dollars 8,000–12,000. However, this estimate corresponds to an experimental production cost, and economies of scale would be expected for industrial production.

Other treatments for perianal fistulas that may be in clinical development have yet to be tested in randomized trials, and so we do not anticipate other products coming onto the market in the near future. Once available, for the reasons outlined earlier in the chapter, we believe the stem cells will fulfill a clear unmet medical need and will help improve the healing and hence the quality of life of patients with anal fistula.

Summary

- Cell therapy has emerged as a new tool to improve wound healing in a number of settings. There are pathological situations in which this cell supply is deficient and wound healing may be delayed or not achieved, this is the case of anal fistula. Stem cells exploit two coordinated biological effects, namely, immunoregulation and the local suppression of inflammation. The promising preclinical and clinical data that we will review in this chapter suggest that stem cells could represent a major advance in the clinical management of this difficult problem.
- With cell therapy, there is no injury to the anal sphincter because tract resection is not required and repeated doses can be used to increase the chance of healing. Importantly, in a clinical setting, fat appears as a great source of stem cells.
- The immunoregulation effect and the local suppression of inflammation, make of patients with perianal Crohn's disease perfect candidates for this treatment.
- For the reasons outlined in this chapter, we believe the stem cells will fulfill a clear unmet medical need and will help improve the healing and hence the quality of life of patients with anal fistula.

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