REVIEW ARTICLE

INDEX COPERNICUS INTERNATIONAL

Mesenchymal stem cells for the treatment of complex perianal fistulas in patients with Crohn disease

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

Katarzyna Borycka-Kiciak[1AEF], Anna Pietrzak[2,3EF], Maciej Kielar[4,5AF], Wiesław Tarnowski[1A]

[1]Department of General and Gastrointestinal Surgery, Orlowski Hospital, Centre of Postgraduate Medical Education, Warsaw, Poland
[2]Department of Gastroenterology, Hepatology and Clinical Oncology, Centre of Postgraduate Medical Education, Warsaw, Poland
[3]Department of Oncological Gastroenterology Institute of Oncology, Warsaw, Poland
[4]Department of Oncology and Nursing Oncology, Institute of Nursing and Obstetrics, Faculty of Medicine and Health Sciences, Jan Kochanowski University, Kielce, Poland
[5]Department of General Surgery, Medicover Hospital, Warsaw, Poland

Article history: Received: 24.04.2019 Accepted: 10.06.2019 Published: 16.06.2019

ABSTRACT: Treatment of perianal fistulizing Crohn's disease is demanding and burdened with a high percentage of failures, which forces clinicians to search for new, more effective therapeutic options. One of these options is the use of adipose-derived mesenchymal stem cells in local administration. Due to their multipotentiality and complex mechanism of action, stem cells are the promising new therapeutic approach for the treatment-refractory complex perianal fistulas – demonstrating both high efficacy and a favorable safety profile. The paper presents current knowledge on the mechanisms of action and manner of administration of mesenchymal stem cells, as well as the effectiveness and safety of their use in the treatment of perianal Crohn's disease based on available literature

KEYWORDS: Crohn's disease, inflammatory bowel disease, mesenchymal stem cells, perianal fistula, treatment

INTRODUCTION

Stem cells and their unique characteristics have been within the scope of interest of both researchers as well as clinicians from numerous fields of medicine. Promising results of stem cell transplantation in plastic and reconstructive surgery, treatment of leukemias, lymphomas, congenital disorders of the immune system, some inherited disorders or malignancies have been reported to date. There are ongoing studies on novel applications of stem cells in the treatment of type 1 diabetes, multiple sclerosis, Parkinson's disease, epilepsy, or autism.

Thus, it is not surprising that Crohn's disease might be a promising therapeutic option. Several dozen studies available in professional literature indicate that systemic administration (intravenous transplantation) of stem cells induces clinical remission in as much as 76% and endoscopic remission in 30% of patients with active luminal Crohn's disease [1]. There are also high hopes associated with local stem cell administration in the treatment of perianal disease. This most severe presentation of the disease, manifesting with numerous, often complex perianal fistulas, remains a great therapeutic challenge. Despite the availability of surgical techniques and undeniable value of biological therapy, therapeutic failure rates still reach 40% and the need for repeated surgical intervention (in over 90% of cases) determines poor prognosis and, on numerous occasions, stoma formation. However, research shows that the use of stem cells [2] enables healing of over 57% of fistulas, including the most difficult cases in patients who have undergone repeated treatment without satisfactory effect.

What are stem cells? Where is their potential hidden? Can they fulfill surgeons' expectations for an optimal (safe and effective) treatment method of perianal fistulas formed in the course of Crohn's disease? Will they finally find their place in the guidelines?

The goal of this work is to present the current results of treatment of complex fistulas formed in the course of perianal Crohn's disease using stem cells and to answer questions regarding their role in the standards of treatment of perianal Crohn's disease.

WHAT ARE STEM CELLS?

Stem cells are multipotential, unspecialized precursor cells characterized by a unique ability to differentiate into cells of various tissues [3, 4]. They affect the growth of normal tissues as well as their repair in case of damage.

We distinguish several types of stem cells depending on their ability to differentiate:

- totipotent cells – possess the ability to transform into all types of cells found in the body, including extraembryonic cells (placenta, umbilical cord) (human embryonic cells from a single blastomere, ESC);
- pluripotent cells – possess the ability to differentiate into all types of cells except for extraembryonic cells; they arise from an embryoblast of a blastocyst;
- multipotent cells – possess the ability to form several types of cells, differentiate within one of the three germ layers: ectoderm, endoderm and mesoderm;
- unipotent cells – can differentiate into one, predefined type of cell (Fig. 1a.).

Contrary to embryonic stem cells, which can only be found in human embryos, somatic (adult-type) stem cells (ASC – adult stem cells) are widely available in the body and constitute an easily accessible biological material. Among several types of cells, those originating from mesodermal germ layer (Fig. 1b.) – mesenchymal stem cells (MSC), are most often utilized in therapeutics. Adult mesenchymal stem cells possess the ability to proliferate and differentiate into various types of tissues, thus stimulating growth and tissue regeneration. They produce and excrete a number of

DOI: 10.5604/01.3001.0013.2390

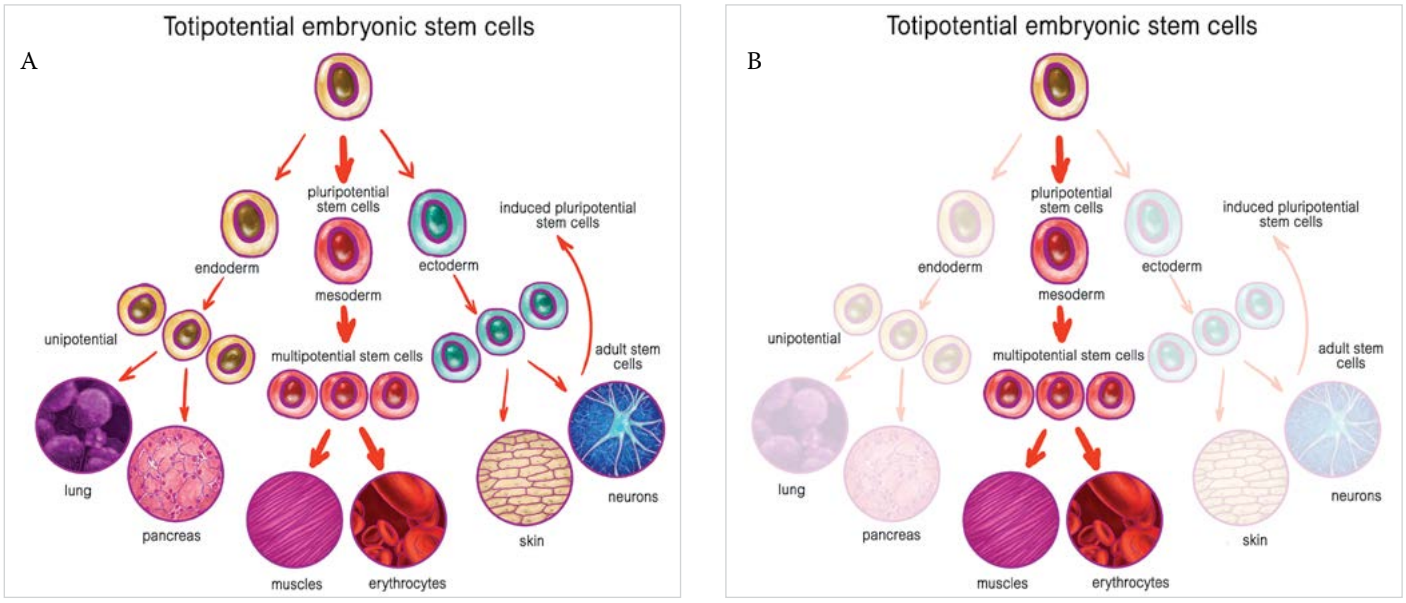

Fig. 1. Stem cell types and differentiation capabilities (a); mesodermal cells are used for therapeutic purposes (b).

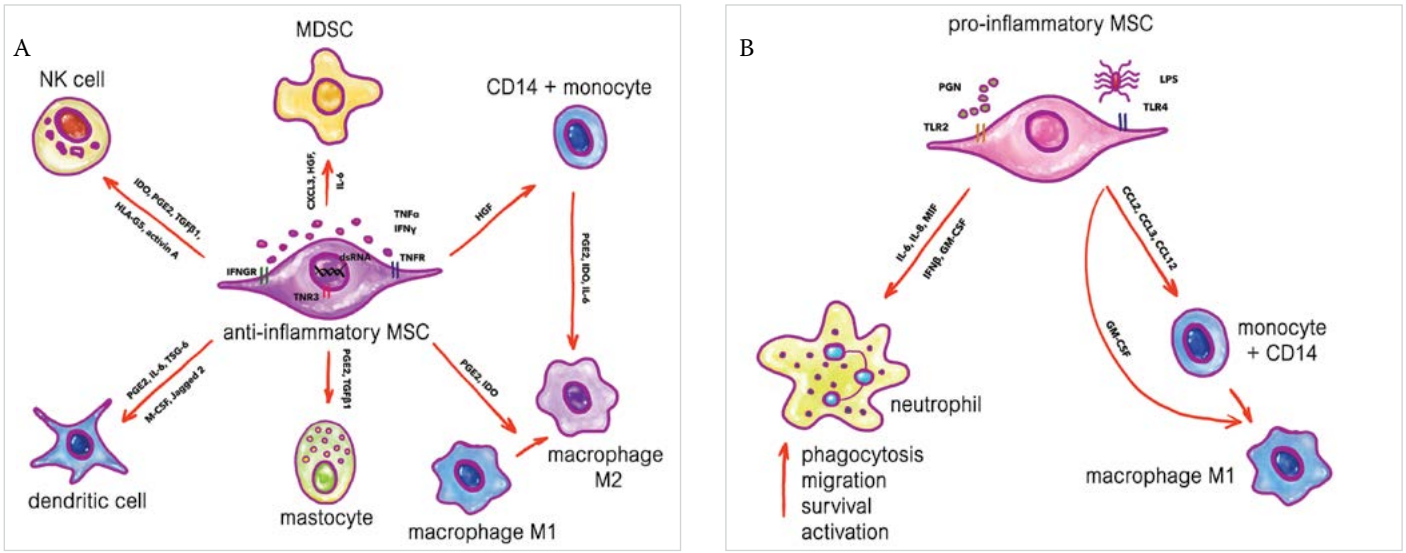

Fig. 2. Activity of mesenchymal stem cells depending on a microenvironment a.) anti-inflammatory phenotype, b.) pro-inflammatory phenotype. MSC – mesenchymal stem cell; MDSC – myeloid-derived suppressor cell; NK cell – natural killer cell; Il-6 – interleukin 6, Il-8 – interleukin 8; HGF – hepatocyte growth factor; TNF-alfa – tumor necrosis factor a' TNFR – TNFa receptor; PGE2 – prostaglandin E2; IDO – indoleamine 2,3-dioxygenase; IFN-g – interferon g; CXCL3 – chemokine (C-X-C motif) ligand 3; CCL2, CCL3, CCL12 – chemokine (C-C motifs) ligands 2, 3 and 12; TGF-b1 – transforming growth factor b1; TSG-6 – tumor necrosis factor-inducible gene 6; GM-CSF – granulocyte macrophage–colony stimulating factor; TLR2, TLR4 – toll-like ligand receptors (2 and 4); MIF – macrophage inhibitory factor; LPS – lipopolysaccharide.

active substances (growth factors, cytokines, chemokines, microRNA, exosomes), which interact with various components of the immunological system, modulating its activity [3–7]. Their immunomodulatory properties determine the ability to suppress inflammation, stimulate angiogenesis, and promote healing. Phenotype of differentiated stem cell depends on its environment – inflammatory microenvironment determines an anti-inflammatory phenotype (Fig. 2a.), while new trauma– pro-inflammatory phenotype (Fig. 2b.). This plasticity of mesenchymal stem cells is decisive to their therapeutic potential in countless indications.

Mesenchymal stem cells can be obtained from the body in several ways (Fig. 3.). Adipose tissue is an easily accessible source of relatively homogenous mix with stable phenotype and high vitality. Both autologous (cells collected from the same patient, usually from the abdomen, thighs or buttocks) as well as ready-made allogenic cells (collected from healthy donors, proliferated under laboratory conditions and delivered as a preparation containing cells of specified number and viability) are used in the treatment of fistulas in Crohn's disease.

In the literature, the number of MSCs in a single administration during a procedure ranges from 200 thousand to 5 mln/mL and from 10 to 120 mln/procedure [8–18]. However, it is known that the efficacy depends on both the number as well as the quality of transplanted cells. A preparation of allogenic adipose-derived mesenchymal stem cells (darvadstrocel) contains 5 mln cells/mL and it is recommended that 24 mL of preparation (120 mln cells/procedure) should be given during a single administration.

CLINICAL PROBLEM

The problem of perianal pathology affects one in three patients with Crohn's disease [19, 20]. In nearly 50% of cases perianal

lesions are present at the time of diagnosis. However, due to great variability of clinical manifestations they are often unrecognized as an integral part of the disease picture and remain untreated for a long time. Perianal fistulas are considered the most severe form of Crohn's disease [20, 21]. Lesions appear and progress suddenly, often over the course of several days, often preceding the symptoms of luminal disease during the exacerbation phase. When treated, they heal with difficulty, leaving permanent marks that impair patients' quality of life in long-term.

Perianal Crohn's disease can manifest as ulcerations (54%), fistulas (42%), fissures, or anal canal stenosis, skin tags, as well as inflammation of varying extent and severity (Fig. 4 a.–f.) [22]. In over a half of patients ulcerations coexist with fistulas – it is the most common presentation of this disease.

Perianal disease phenotype is not related to a specific location or extent of intestinal lesions, but its prevalence increases with more distal gastrointestinal involvement. It is diagnosed in 90% of cases of rectal involvement and in 12% of cases of disease located in the small intestine [20, 23]. Frequency of perianal disease is also related to the duration of underlying disease. The longer the history of Crohn's disease, the more likely it is that perianal lesions will manifest (they are noted in 15% of patients with a 5-year history of Crohn's disease and in 25% of patients with disease duration more than 20 years) [20, 24].

Fistulas pose the greatest therapeutic challenge in perianal disease. Usually high and branched [25, 26] (Fig. 5.) with internal orifices located at any place in the anal canal or rectum, they elude the Parks classification used to date [27].

Classification of the American Gastroenterology Association (AGA) is used to describe them in practice, dividing fistulas into simple and complex and taking into consideration, aside from its relation to the external sphincter, the number of external orifices, presence of other complications (such as ulcers, anal stenosis, proctitis), as well as involvement of neighboring structures and organs [28].

Detailed physical examination complemented by magnetic resonance imaging of the pelvis or transrectal US (if no anal stricture is present) allows for precise determination of the course of fistulas and their location relative to anal sphincters, thus enabling proper treatment planning.

WHAT DO WE CURRENTLY HAVE AT OUR DISPOSAL IN THE TREATMENT OF PERIANAL CROHN'S DISEASE?

Principles of surgical treatment state that simple, low, asymptomatic fistulas can be treated with fistulotomy (canal dissection) or fistulectomy (excision of a fistula). That does not, however, apply to Crohn's disease. Fistulas formed in the course of Crohn's disease, even with the simplest course, are treated as complex. In most cases they are symptomatic, high, often branched, with areas of retention and accompanied by inflammation of the rectum and surrounding tissues.

The first and fundamental element of management of perianal fistulas in the course of Crohn's disease involves controlling sepsis in the region (Fig. 7.). Surgical drainage of abscesses and retention areas (>2 cm) over the course of fistula and and drainage of the fistula itself are necessary. A loose seton inserted in the main fistula canal and left for many weeks or even months enables control of the septic process over the course of treatment. Antibiotics: metronidazole (750–1500 mg/day) and ciprofloxacin (500–1000 mg/day) in short-term (1–2 weeks) and long-term

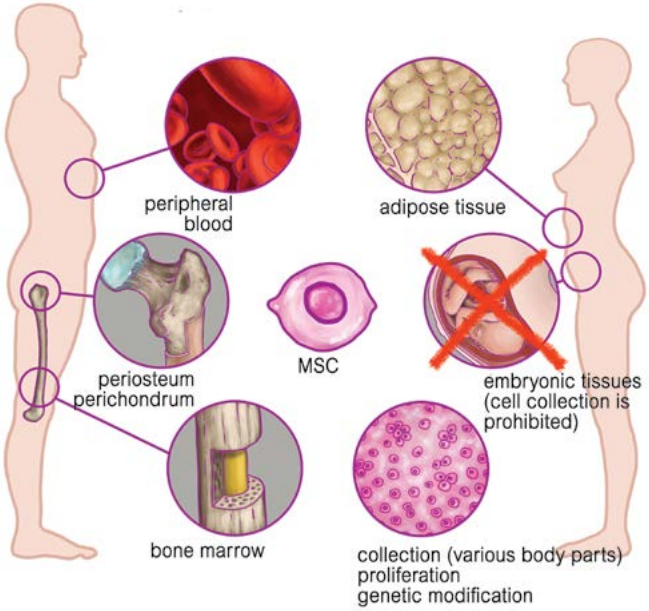

Fig. 3. Sources of stem cells.

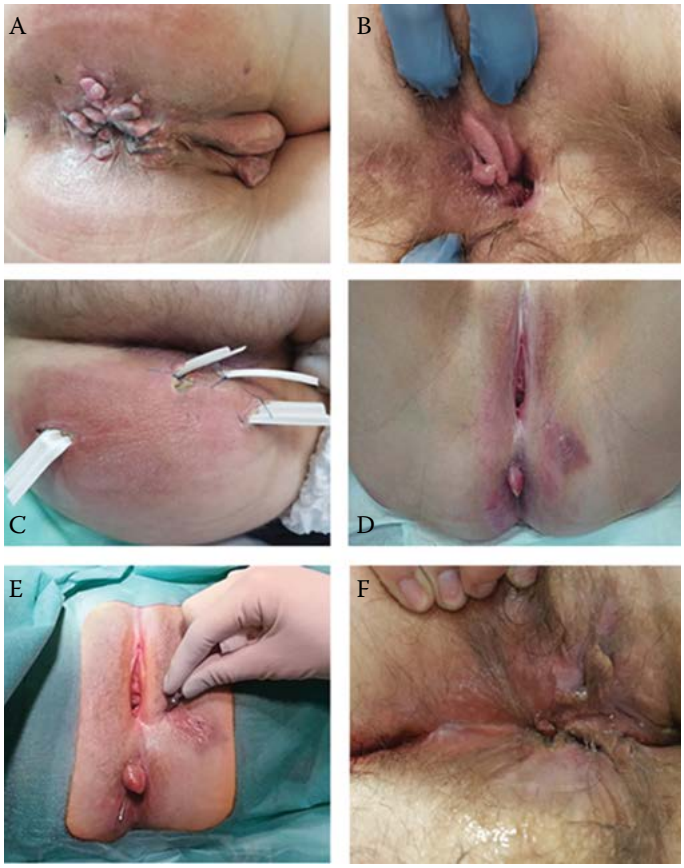

Fig. 4. Perianal lesions in the course of Crohn's disease a.) skin tags b.) ulceration with complex fistula c.) perianal abscess with fistula d.) inflammation (dermatitis) around the anus with external opening of a fistula visible in the left anterior quadrant e.) canal of complex fistula f.) anal stenosis.

Tab. I. Previously published and ongoing studies on local application of mesenchymal stem cells in the treatment of perianal fistulas in the course of Crohn's disease.

LP	AUTHOR	YEAR	TYPE OF STUDY	INTERVENTION	TYPE AND SOURCE OF CELLS	HEALING EFFICACY (%)	SAFETY
1	Garcia-Olmo i wsp. [44]	2003	Case report	Local injection	Autologous adipose tissue	100%	Perianal abscesses / proctalgia
2	Garcia-Olmo et al. [8]	2005	Phase I	Local injection of $3x10^6$ stem cells		75% after 8 weeks	
3	Garcia-Olmo et al. [9]	2009	Phase II b	Local injection of $2x10^6$ stem cells+ glue vs. glue alone		71% after 8 weeks	
4	Cho et al. [10]	2013	Phase I	Local injection of $1x10^7$ or $2x10^7$ or $4x10^7$		30% after 8 weeks	
5	Lee et al. [12]	2013	Phase II	Local injection $3x10^7$ or $6x10^7$		82% after 8 weeks 88% after 1 year	
6	Cho et al. [11]	2015	Phase II	Local injection $9\text{-}42x10^7$		83% after 2 years	
7	Cicciocippo et al. [13]	2011	open	Local injection of $1.5\text{-}3\ x10^7$	Autologous – bone marrow	67% after 8 weeks 100% after 1 year	Perianal abscesses/ proctalgia
8	De la Portilla et al. [14]	2013	Phase II a	Local injection of $2x10^6$ or $4x10^6$	Allogenic – adipose tissue	56.3% after 24 weeks 69.2% improvement	
9	Panes et al. [15]	2016	Phase III	Local injection of $12x10^7$ or placebo	Allogenic – adipose tissue	50% in 24 weeks	
10	Molendijk et al. [17]	2015	open	Local injection of $1x10^7$ or $3x10^7$ or $9x10^7$	Allogenic – bone marrow	20%, 40%, 80%, depending on a dose after 12 weeks	
11	Dietz et al. [18]	2017	Phase I	Local injection of $2x10^6$ on GoreBioA plug	Autologous – adipose tissue	83% after 24 weeks	
12	Panes et al. [16]	2018	Phase III	Local injection	Allogenic – adipose tissue	59% after 52 weeks	
13	Herreros et al. [45]	2012	Phase III	Local injection	Autologous – adipose tissue + tissue glue	57.1% (cells), 52.4% (cells+glue) and 37.3% (glue) after 52 weeks	
14	NCT01915927	-	Phase III	Local injection on a plug	Autologous – adipose tissue + plug	Ongoing	
15	NCT03279081	-	Phase III	Local injection of $12x10^7$ or placebo	Allogenic – adipose tissue	Ongoing; patient recruitment	

(12 weeks in combination with biological therapy) treatment play a significant role in controlling local sepsis [29]. However, studies did not corroborate their efficacy in healing of fistulas [30, 31]. Antibiotics should not be used alone, without prior surgical drainage and adjuvant conservative (biological/immunomodulating) therapy [32].

Use of thiopurines (azathioprine or 6-mercaptopurine) and oral tacrolimus failed to bring expected results; the proportion of total or partial fistula closures (20–40%) does not differ significantly [19, 33]. However, they are often used as part of conservative treatment in conjunction with biological therapy, which proved effective in both induction as well as maintenance of remission of perianal lesions [26, 34–36], bringing break-through in therapy of perianal Crohn's disease. It provides improvement in 86–88% of cases, including complete fistula closure in half of them.

A combination of drainage and optimal conservative treatment based on anti-TNF alpha and immunomodulation/immunosuppression demonstrates higher effectiveness than each of those therapies alone [37, 38]. Unfortunately, due to formation of antibodies against biological agents resulting in loss of clinical response in nearly 50% of patients [36], the effects of this treatment regimen in long-term follow-up are not so good.

Finally, the percentage of clinical remissions on biological therapy is estimated at 48–53% and in only 14–24% of patients fistula closure can be confirmed by imaging studies [39, 40]. Consequently, nearly half of patients resistant to biological therapy require further surgical treatment.

The choice of corrective surgery is difficult. It depends on local conditions, individual situation of a patient, tolerance of conservative treatment and surgeon's experience. Although several surgical techniques are available: from internal orifice closure with a mucosal flap and ligation of intersphincteric fistula tract (LIFT), through fiberoscopic (VAAFT) and laser (FiLAC) methods, to the use of artificial plugs, pastes and tissue glues, none of these methods is perfect. Minimally invasive, sphincter sparing techniques appear to be quite ineffective (34–64% effectiveness, 37% recurrences) [41]. More radical methods pose a risk of additional damage to the sphincters (which are already affected by a long-lasting disease), resulting in the risk of fecal incontinence in this group of patients reaching 59% [42]. At last, patients with many complications significantly affecting their quality of life, often after numerous procedures, are referred for stomy or proctectomy [23].

In this context, the search for novel, alternative therapeutic solutions seems natural. Such solutions should be not only more effective and sparer sphincter function, but also aid their regeneration, accelerate healing and restrict perianal fibrosis, which currently determines poor functional outcome in over 90% of patients due to the necessity of multiple surgical interventions [20].

ARE STEM CELLS THE ANSWER TO OUR NEEDS REGARDING TREATMENT OF FISTULIZING CROHN'S DISEASE?

Even though the pathophysiology of fistula formation in the course of Crohn's disease has not been yet fully elucidated, it is known

that defect of inflamed intestinal endothelium is of key significance for the mechanism of their development [43]. Therefore, mesenchymal stem cells with their anti-inflammatory, immunomodulatory and regenerative potential seemed to present an optimal therapeutic option. This notion has already been substantiated in early phase I and II studies, which demonstrated over 70% fistula closure rate over 8 weeks [8, 9] and 56% rate of complete healing over 6-month follow-up [14].

Many studies assessing the efficacy of mesenchymal stem cells have been published in the literature since then and some of them, especially randomized, placebo-controlled studies with long-term follow-up, are still ongoing (Tab. I.). At first, autologous cells collected from a patient and processed immediately before transplantation were used. Both bone marrow-derived [13] and adipose-derived stem cells [9, 10, 18] showed similar efficacy – 67–71% healing rate during the first 8 weeks and over 80% in 1-year and 2-year follow-up [11, 12]. Currently, most experimental studies utilize cells collected from adipose tissue, mainly due to their broad availability and relatively easy collection procedure free from serious complications (liposuction). However, obtaining fat tissue from a patient with Crohn's disease can be sometimes challenging.

Intensive studies on the use of allogenic mesenchymal stem cells collected from healthy donors and proliferated under laboratory conditions have been going on for several years. The advantage of such a preparation lies in well-defined number of cells of stable phenotype and proper viability per 1 ml of solution. Preliminary results of studies demonstrating their effectiveness in healing difficult, treatment-resistant, complex fistulas in short- and long-term follow-up are already available [15, 16].

Over a 6-month follow-up the percentage of complete remissions confirmed clinically and through imaging (pelvic MRI) reached 51%, clinically confirmed – 57%, and positive response to treatment (improvement by at least 50%) was noted in 70% of patients treated with stem cells [15]. The effect persisted after a year of observation and the proportion of total remissions even increased to 56.3% and of clinical remissions to 59.2% [16].

Such a result in this difficult population of patients with complex fistulas not responding to any conventional treatments seems promising and stem cells might be considered a minimally invasive alternative to currently available treatment. Interestingly, there was also synergistic effect of stem cells with adjuvant treatment despite prior ineffectiveness of the latter – the proportion of remissions obtained in the group of patients treated with biological and immunomodulatory therapy reached 67% compared to 54% in patients without adjuvant treatment of the underlying condition [15].

MSC therapy exhibits higher efficacy than any other method used to date [1, 2] regardless of the origin of cells (adipose tissue or bone marrow, autologous or allogenic), with total recurrence rate not exceeding 16% after 1 year [1].

According to a meta-analysis [46] the rate of disease-free survival after MSC treatment reached 91% during the 1st year, 57% over 3 years and 19% during 5 tears. But do stem cells bring long-term improvement? That remains undetermined. There are no studies evaluating long-term (above 2 years) efficacy of this method.

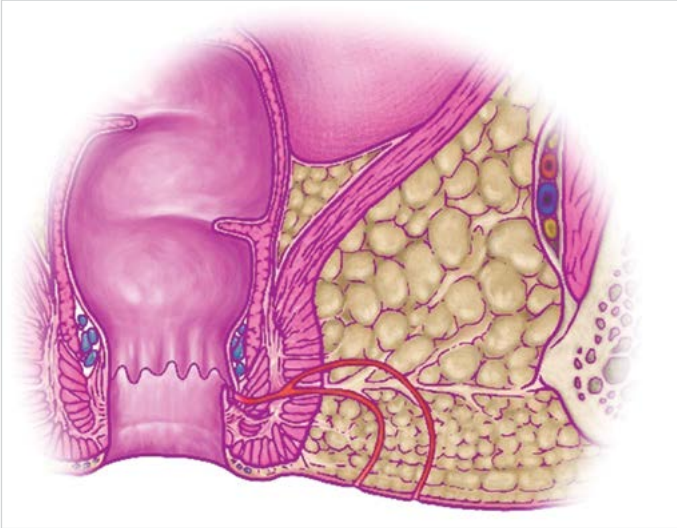

Fig. 5. Complex fistula in the course of Crohn's disease – high (crosses the external anal sphincter above the 1/3 of its height), branched (two external orifices).

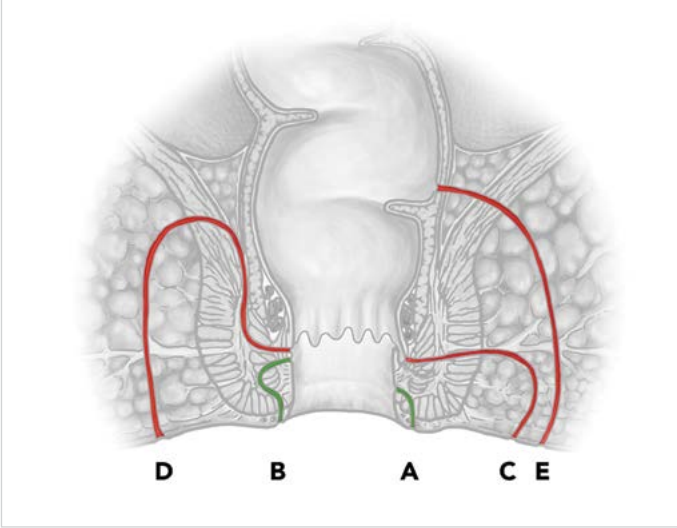

Fig. 6. Classifications of fistulas in the course of Crohn's disease. Parks Classification: A. superficial fistulas (simple) B. intersphincteric (type 1 complex fistula acc. to Parks) C. transsphincteric (type 2 complex fistula acc. to Parks) D. suprasphincteric (type 3 complex fistula acc. to Parks) E. extrasphincteric (type 4 complex acc. to Parks). AGA classification: simple (green) and complex fistulas (red).

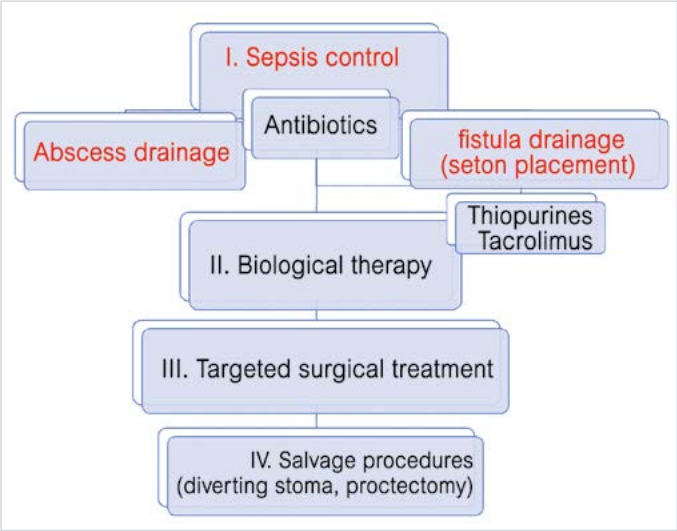

Fig. 7. Scheme of treatment of perianal fistulas in the course of Crohn's disease.

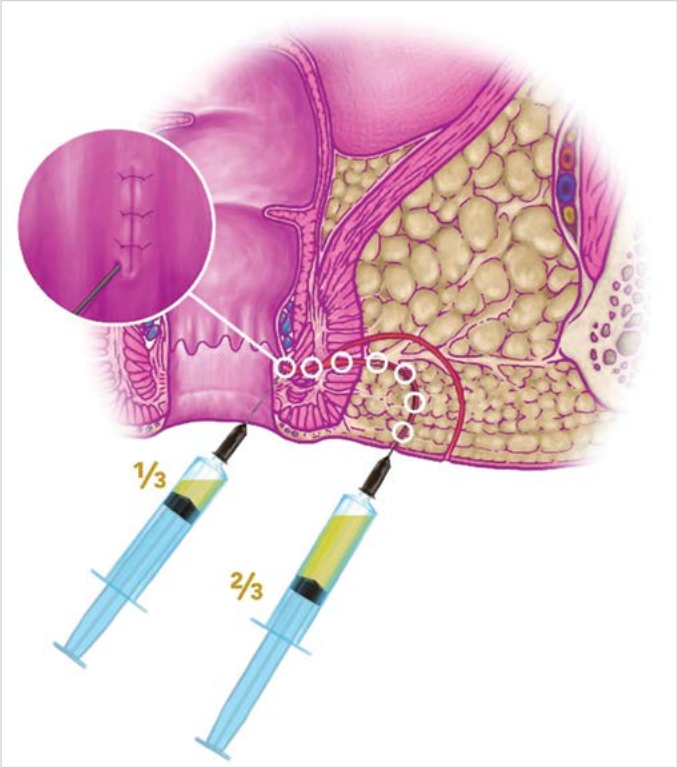

Fig. 8. Stem cell administration procedure.

It is also necessary to assess the effect of intermittent administration of stem cells as maintenance therapy.

SAFETY OF THE METHOD

The percentage of adverse events related to stem cell administration is not high and reaches 17%.

The most commonly reported adverse events associated with stem cell therapy (8–9% rate) include: perianal abscess, proctalgia and pharyngitis. Most of them are not very severe. Serious adverse events are rare and usually related to exacerbation of the underlying illness. Their frequency does not exceed 12%.

Available data shows that mesenchymal stem cells are not toxic, even with multiple administrations. They are not genotoxic and do not have negative impact on reproduction and development of offspring. They also do not seem to affect the processes of neoplastic transformation. All those aspects of stem cell treatment are currently under investigation.

WHAT DOES THE SURGICAL PROCEDURE LOOK LIKE?

Even though procedures of stem cell administration to the fistula have been performed for several years, only lately a uniform, validated surgical protocol has been established [47].

Exact localization and classification of a fistula is of key importance before planned surgical procedure. Therefore, it is necessary to perform detailed physical examination under anesthesia, with possible drainage of abscesses and areas of retention within the fistula or thread drainage of a wide fistula canal.

Local treatment of inflammatory rectal lesions and antibiotic therapy typical for Crohn's disease (metronidazole 3x500 mg and ciprofloxacin 2x500 mg p.o. for 7–10 days) can be continued during the postoperative period. Anal stenosis does not subside with conservative treatment and should be managed by endoscopic dilatation.

The surgical procedure involving local stem cell administration is conducted under subarachnoid or general anesthesia in gynecological position and lasts about 30–40 minutes.

The first and fundamental stage involves careful curettage of all fistula canals all the way to the internal orifice in order to remove epithelial lining and necrotic tissues. Bloody discharge from the canal indicates that the canal was cleaned properly. This stage ends with copious washing of all fistula canals with physiological saline.

Closure of the internal orifice is an important step in the procedure. If possible, it should be performed using simple, tight, continuous stitch with dissolvable suture (monofilament 2.0 or 3.0), facilitating the third stage of surgical procedure – local administration of stem cells (Fig. 8.). Solution containing stem cells (autologous or allogenic) is injected into the submucosa surrounding internal orifice (about 1/3–1/2 of the total volume of the preparation) and intramurally along the entire length of the fistula.

The procedure ends with placing a loose dressing without leaving a seton in the rectum and without administration of disinfectants or other agents that might be toxic to the stem cells (hydrogen peroxide is particularly contraindicated).

DID STEM CELLS FULFILL OUR EXPECTATIONS?

Our search for new methods of perianal Crohn's disease focuses not only on the safety and effectiveness in inducing healing of fistulas, especially the complex types. Such a method should also be able to maintain remission and be characterized by low proportion of recurrences in long-term follow-up; it should spare the sphincters and, optimally, even facilitate their regeneration following injury caused by previous interventions and underlying disease. Reduction of fibrosis in this difficult region and possibly even improved healing of other perianal lesions would be desirable. The surgical procedure itself should be simple and repeatable, resulting in broader availability.

Literature reports imply that local administration of mesenchymal stem cells fulfills a significant part of those postulations. Stem cells are effective in over a half of most difficult cases, where previous methods were proven unsuccessful, and their results persist over a 2-year follow-up. The risk of adverse events is relatively low, and no adverse effects related to the stem cells themselves have been reported. Surgical procedure is relatively easy and, if performed correctly, ensures preservation of sphincter. Studies in experimental models demonstrated efficacy of MSCs in intensification of healing through promotion of re-epithelialization, cell proliferation and enhanced angiogenesis [48, 49]. Available histopathological studies of tissues collected from areas of stem cell administration 1 month and 2 years after MSC treatment [50] confirm significant increase in the number of collagen fibers and fibroblasts, presence of structurally normal stratified epithelium and compact smooth muscle layer with multidirectional arrangement of fibers in the absence of any signs of rejection of transplanted MSCs. It suggests that there

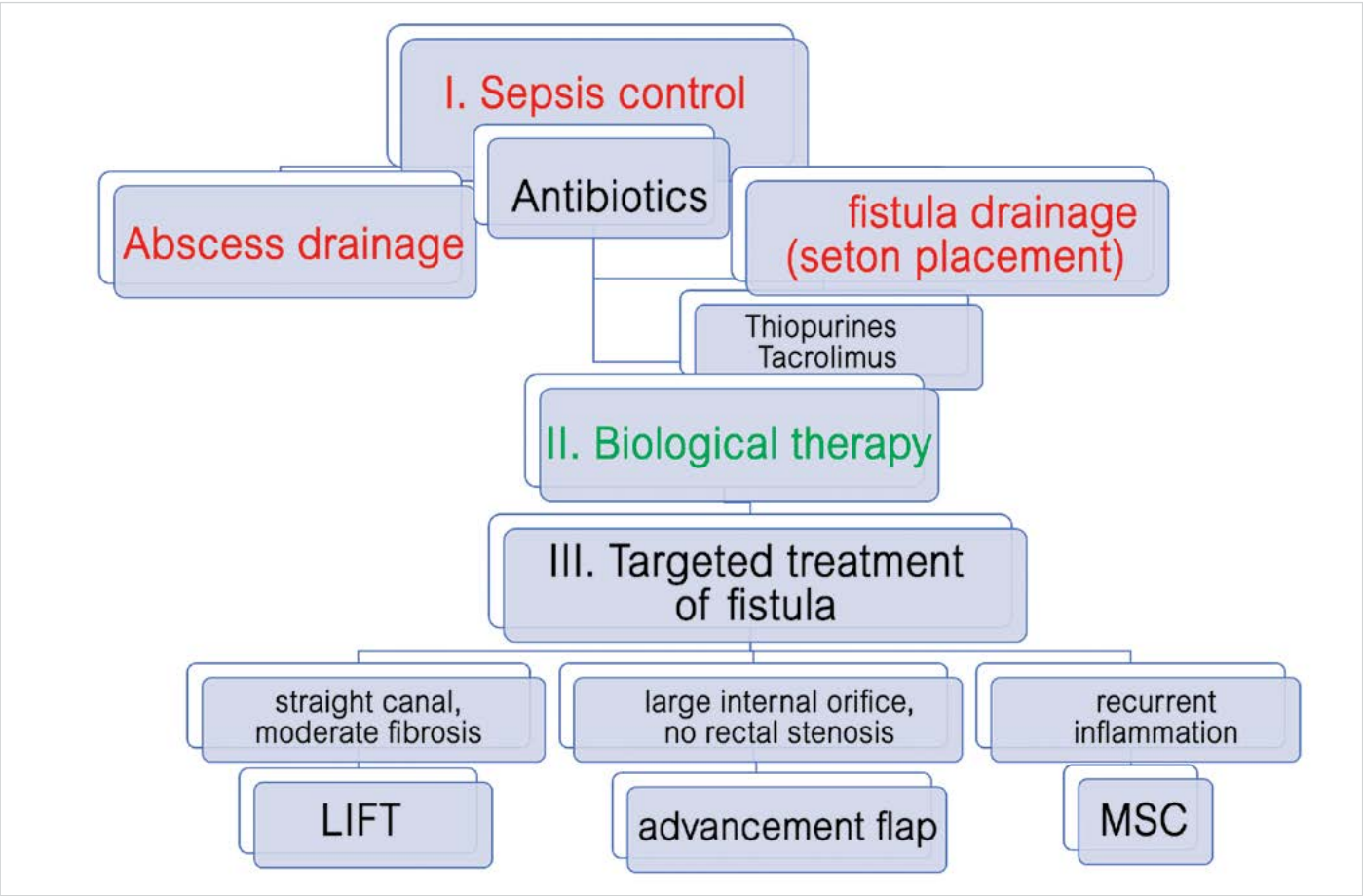

Fig. 9. Therapeutic algorithm for treatment of fistulas in the course of Crohn's disease taking into consideration stem cell treatment (acc. to Bouchard 2018).

is a chance for positive long-term outcomes of stem cell treatment on perianal tissue healing and sphincter function in a near future.

However, analysis of literature and clinical observation imply that the therapeutic potential of stem cells has not been fully utilized. From a surgical point of view the main limitation of the method of stem cell administration in the perianal region is related to the fluid consistency of the preparation, causing incalculable losses of biological material during injection and resulting in low numbers of surviving cells being administered into the fistula. It significantly limits bioavailability of stem cells and hence, effectiveness of the procedure. Stem cells do not have enough structural support and access to nutrients to allow survival during the first few days before they are reached by newly formed vessels and are able to demonstrate their full potential.

First therapeutic algorithms [32] taking into consideration treatment with mesenchymal stem cells and defining indications for their use have already been published (Fig. 9.). Nevertheless, determining the optimal profile of a patient suitable for this kind of therapy is still a matter of time.

Further studies are required to standardize the technique of stem cell administration into the canals of branched fistulas and to determine the optimal doses and injection sites for best therapeutic effect.

Summarizing, there are still many uncertainties regarding use of MSCs, but it is undoubtedly one of the most promising therapeutic options for the treatment of perianal Crohn's disease. We still don't know the answers to many questions and the studies are ongoing. Time, larger numbers of patients and greater experience are required to evaluate the place of stem cells in the standards of treatment.

CONCLUSIONS

Due to their multipotential nature, plasticity, immunoregulatory and regenerative properties as well as relatively easy accessibility mesenchymal stem cells demonstrate great therapeutic potential in the treatment of perianal Crohn's disease. When used as local injections following appropriate surgical preparation of a fistula, they constitute a promising tool for management of treatment-resistant perianal fistulas, characterized by high therapeutic efficacy and favorable safety profile.

At the moment, however, we do not have enough scientific evidence to form unequivocal opinion regarding use of stem cells in the treatment of perianal Crohn's disease.

Available results of research are encouraging, but do not provide answers to all questions and are not fully conclusive. Answers should become available in the coming years. Undoubtedly, information obtained from ongoing and future studies should revolutionize our approach to the treatment of perianal fistulas in the course of Crohn's disease.

REFERENCES:

1. Qiu Y., Li M.Y., Feng T., Feng R., Mao R., Chen B.L., He Y., Zeng Z.R., Zhang S.H., Chen M.H.: Systematic review with meta-analysis: the efficacy and safety of stem cell therapy for Crohn's disease Stem Cell Res Ther., 2017; 8(1): 136.
2. Lightner A.L., Wang Z., Zubair A.C., Dozois E.J.: A Systematic Review and Meta-analysis of Mesenchymal Stem Cell Injections for the Treatment of Perianal Crohn's Disease: Progress Made and Future Directions. Dis Colon Rectum., 2018; 61(5): 629–640.
3. Kolf C.M., Cho E., Tuan R.S.: Mesenchymal stromal cells. Biology of adult mesenchymal stem cells: regulation of niche, self-renewal and differentiation. Arthritis Res Ther., 2007; 9(1): 204.
4. Le Blanc K., Davies L.C.: Mesenchymal stromal cells and the innate immune response. Immunol Lett. 2015; 168(2): 140–146.
5. Le Blanc K., Mougiakakos D.: Multipotent mesenchymal stromal cells and the innate immune system, Nat. Rev. Immunol., 2012; 12: 383–396.
6. Chen X., Armstrong M.A., Li G.: Mesenchymal stem cells in immunoregulation. Immunol Cell Biol, 2006; 84: 413–421.
7. Lin L., Du L.: The role of secreted factors in stem cells-mediated immune regulation. Cell Immunol., 2018; 326: 24–32.
8. Garcia-Olmo D., Garcia-Arranz M., Herreros D. i wsp.: A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. Dis Colon Rectum., 2005; 48: 1416–1423.
9. Garcia-Olmo D., Herreros D., Pascual M. i wsp.: Treatment of enterocutaneous fistula in Crohn's Disease with adipose-derived stem cells: a comparison of protocols with and without cell expansion. Int J Colorectal Dis., 2009; 24: 27–30.
10. Cho Y.B., Lee W.Y., Park K.J. i wsp.: Autologous adipose tissue-derived stem cells for the treatment of Crohn's fistula: a phase I clinical study. Cell Transplant., 2013; 22: 279–285.
11. Cho Y.B., Park K.J., Yoon S.N. i wsp.: Long-term results of adipose-derived stem cell therapy for the treatment of Crohn's fistula. Stem Cells Transl Med., 2015; 4: 532–537.
12. Lee W.Y., Park K.J., Cho Y.B. i wsp.: Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Crohn's fistula. Stem Cells., 2013; 31: 2575–2581.
13. Ciccocioppo R., Bernardo M.E., Sgarella A. i wsp.: Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease. Gut., 2011; 60: 788–798.
14. De la Portilla F., Alba F., Garcia-Olmo D. i wsp.: Expanded allogeneic adiposederived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial. Int J Colorectal Dis., 2013; 28: 313–323.
15. Panés J., García-Olmo D., Van Assche G. et al.: Expanded allogeneic adiposederived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. Lancet., 2016; 388: 1281–1290.
16. Panés J., García-Olmo D., Van Assche G., Colombel J.F., Reinisch W., Baumgart D.C., Dignass A., Nachury M., Ferrante M., Kazemi-Shirazi L., Grimaud J.C., de la Portilla F., Goldin E., Richard M.P., Diez M.C., Tagarro I., Leselbaum A., Danese S.: ADMIRE CD Study Group Collaborators. Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients with Crohn's Disease. Gastroenterology, 2018; 154(5): 1334–1342.e4.
17. Molendijk I., Bonsing B.A., Roelofs H. i wsp.: Allogeneic bone marrow-derived mesenchymal stromal cells promote healing of refractory perianal fistulas in patients with Crohn's disease. Gastroenterology, 2015; 149: 918–927.e6.
18. Dietz A.B., Dozois E.J., Fletcher J.G., Butler G.W., Radel D., Lightner A.L., Dave M,, Friton J., Nair A., Camilleri E.T., Dudakovic A., van Wijnen A.J., Faubion W.A.: Autologous Mesenchymal Stem Cells, Applied in a Bioabsorbable Matrix, for Treatment of Perianal Fistulas in Patients With Crohn's Disease. Gastroenterology, 2017; 153(1): 59–62. e2.
19. Sandborn W.J., Present D.H., Isaacs K.L. i wsp.: Tacrolimus for the treatment of fistulas in patients with Crohn's disease:6 Canadian Journal of Gastroenterology and Hepatology a randomized, placebo-controlled trial. Gastroenterology, 2003; 125(2): 380–388.
20. Schwartz D.A., Loftus E.V. Jr, Tremaine W.J. et al.: The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology, 2002; 122: 875–880.
21. Tang L.Y., Rawsthorne P., Bernstein C.N.: Are perineal and luminal fistulas associated in Crohn's disease? A population-based study. Clin Gastroenterol Hepatol., 2006; 4(9): 1130–1134.
22. Wallenhorst T., Brochard C., Bretagne J.F., Bouguen G., Siproudhis L.: Crohn's disease: is there any link between anal and luminal phenotypes? Int J Colorectal Dis., 2016; 31(2): 307–311.
23. Gecse K.B., Bemelman W., Kamm M.A. et al.: A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut., 2014; 63: 1381–1392.
24. Eglinton T.W., Barclay M.L., Gearry R.B., Frizelle F.A.: The spectrum of perianal Crohn's disease in a population-based cohort. Dis Colon Rectum, 2012; 55: 773–777.
25. Rankin G.B., Watts H.D., Melnyk C.S., Kelley M.L. Jr.: National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications, Gastroenterology, 1979; 77(4): 914–920.
26. Sands B.E., Anderson F.H., Bernstein C.N., Chey W.Y., Feagan B.G., Fedorak R.N. i wsp.: Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med., 2004; 350(9): 876–885.
27. Parks A.G., Gordon P.H., Hardcastle J.D.: A classification of fistula in ano. British Journal of Surgery, 1976; 63(1): 1–12.
28. American Gastroenterological Association Clinical Practice Committee: American Gastroenterological Association medical position statement: perianal Crohn's disease. Gastroenterology, 2003; 125(5): 1503–1507.
29. Dewint P., Hansen B.E., Verhey E. i wsp.: Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo-controlled trial (ADAFI). Gut, 2014; 63: 292–299.
30. Prantera C., Berto E., Scribano M.L., Falasco G.: Use of antibiotics in the treatment of active Crohn's disease: experience with metronidazole and ciprofloxacin. Italian Journal of Gastroenterology and Hepatology, 1998; 30(6): 602–606.
31. Thia K.T., Mahadevan U., Feagan B.G. i wsp.: Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double–blind, placebo–controlled pilot study, Inflammatory Bowel Diseases, 2009; 15(1): 17–24.
32. Bouchard D., Pigot F., Staumont G., Siproudhis L., Abramowitz L., Benfredj P., Brochard C., Fathallah N., Faucheron J.L., Higuero T., Panis Y., de Parades V., Vinson-Bonnet B., Laharie D.: Management of anoperineal lesions in Crohn's disease: a French National Society of Coloproctology national consensus. Tech Coloproctol., 2018; 22(12): 905–917.
33. Pearson D.C., May G.R., Fick G.H., Sutherland L.R.: Azathioprine and 6-mercaptopurine in Crohn disease. A Metaanalysis. Annals of Internal Medicine, 1995; 123(2): 132–142.
34. Colombel J.F., Schwartz D.A., Sandborn W.J. i wsp.: Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut, 2009; 58(7): 940–948.
35. Hinojosa J., Gomollón F., García S., Bastida G., Cabriada J.L., Saro C., Ceballos D., Peñate M., Gassull M.A.: Spanish Scientific Group on Crohn's Disease and Ulcerative Colitis. Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: a prospective, open label, multicentre trial. Aliment Pharmacol Ther., 2007; 25(4): 409–418.
36. Duff S., Sagar P.M., Rao M., Dolling S., Sprakes M., Hamlin P.J.: Infliximab and surgical treatment of complex anal Crohn's disease. Colorectal Dis, 2012; 14: 972–976.
37. El-Gazzaz G., Hull T., Church J.M.: Biological immunomodulators improve the healing rate in surgically treated perianal Crohn's fistulas. Colorectal Dis, 2012, 14: 1217–1223.
38. Hyder S.A., Travis S.P., Jewell D.P., Mortensen N.J.M., George B.D.: Fistulizing anal Crohn's disease: results of combined surgical and infliximab treatment. Dis Colon Rectum, 2006; 49: 1837–1841.
39. Erzin Y., Ercaliskan K., Hatemi I., Atay K., Bozcan S., Demir N., Celik A.: P334 Evolution of a long-term follow-up cohort of Crohn's disease with complex perianal fistula: from antibiotic to combined AZA and anti-TNF based treatment ending up clinical and radiological healing with or without stoma. J Crohns Colitis, 2016; 10 Suppl: S262.
40. Erzin Y., Ercaliskan A., Hatemi I., Eyice D., Baca B., Demir N., Celik A.: P295 What is our success on complex perianal fistula healing in the clinic? From antibiotic to combined anti-TNF based treatment, ending with or without ileostomy. J Crohns Colitis, 2014; 8 Suppl: S186–S187.
41. Soltani A., Kaiser A.M.: Endorectal advancement flap for cryptoglandular or Crohn's fistula-in-ano. Dis Colon Rectum., 2010; 53(4): 486–495.
42. Panes J., Reinisch W., Rupniewska E., Khan S., Forns J., Khalid J.M., Bojic D., Patel H.: Burden and outcomes for complex perianal fistulas in Crohn's disease: Systematic review. World J Gastroenterol., 2018, 24(42): 4821–4834.

43. Scharl M., Rogler G.: Pathophysiology of fistula formation in Crohn's disease. World J Gastrointest Pathophysiol, 2014; 5: 205–212.
44. García-Olmo D., García-Arranz M., García L.G., Cuellar E.S., Blanco I.F., Prianes L.A., Montes J.A., Pinto F.L., Marcos D.H., García-Sancho L.: Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: a new cell-based therapy. Int J Colorectal Dis., 2003; 18(5): 451–454.
45. Herreros M.D., Garcia-Arranz M., Guadalajara H., De La-Quintana P., Garcia-Olmo D.: Autologous expanded adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistulas: a phase III randomized clinical trial (FATT 1: fistula advanced therapy trial and long-term evaluation), Diseases of the Colon and Rectum., 2012; 55(7): 762–772.
46. Burt R.K., Craig R.M., Milanetti F. i wsp.: Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. Blood., 2010; 116: 6123–6132.
47. Molendijk I. van der Meulen-de Jong A.E., Verspaget H.W., Veenendaal R.A., Hommes D.W., Bonsing B.A., Peeters K.C.M.J.: Standardization of mesenchymal stromal cell therapy for perianal fistulizing Crohn's disease. Eur J Gastroenterol Hepatol. 2018; 30(10): 1148–1154.
48. Wu Y., Chen L., Scott P.G., Tredget E.E.: Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis. Stem Cells., 2007; 25: 2648–2659.
49. Chen L., Tredget E.E., Wu P.Y., Wu Y.: Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing PLoS ONE., 2008; 3: e1886–1894.
50. García-Arranz M., Gómez-Pinedo U., Hardisson D., Herreros D., Guadalajara H., García-Gómez I., García-Verdugo J.M., García-Olmo D.: Histopathological analysis of human specimens removed from the injection area of expanded adipose-derived stem cells. Histopathology, 2010; 56(7): 979–982.

Liczba słów: 5310 Liczba stron: 10 Tabele: 1 Ryciny: 9 Piśmiennictwo: 50

DOI: 10.5604/01.3001.0013.2390 Table of content: https://ppch.pl/issue/12552

Competing interests: The authors declare that they have no competing interests.

Corresponding author: Katarzyna Borycka-Kiciak MD PhD; Department of General and Gastrointestinal Surgery, Orlowski Hospital, Centre of Postgraduate Medical Education; Czerniakowska Street 231 00-416 Warsaw, Poland; Phone: +48 22 58 41 130; E-mail: kborycka@interia.pl

Cite this article as: Borycka-Kiciak K., Pietrzak A., Kielar M., Tarnowski W.: Mesenchymal stem cells for the treatment of complex perianal fistulas in patients with Crohn disease; Pol Przegl Chir 2020: 92 (1): 38–47