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PHARMACOCLINICAL PROTOCOL FOR THE USE OF DARVADSTROCEL IN THE TREATMENT OF COMPLEX PERIANAL FISTULAS IN CROHN'S DISEASE IN THE NATIONAL HEALTH SYSTEM

Approved by the Permanent Pharmacy Commission

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All the experts have made a conflict of interest declaration

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1. INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease in which any part of the gastrointestinal tract can be affected [(1)].

Multiple indexes have been designed with the aim of quantifying the inflammatory activity of the affected intestine, with the CDAI *(Crohn's Disease Activity Index)* the most used in clinical trials. According to this, patients with symptomatic remission would have a CDAI <150, those with mild-moderate disease, between 150-220, moderate to severe 220-450 and those with very severe or life-threatening CD would correspond to a value greater than 450[(2)].

Perianal fistulas are common manifestations in CD (may affect 15-50% of patients) and consist of abnormal communications between the anal canal or rectum and the skin in the perianal area, originating from CD ulcers that spread to neighbouring structures [(3)].

The most commonly used clinical classification is based on the one proposed by the AGA *(American Gastroenterology Association),* that divides them into simple or complex. A complex fistula is defined as one that affects both anal sphincters (high transsphincteric, extrasphincteric or suprasphincteric), it may present more than one internal orifice, with secondary paths, anal stenosis, collections or it may fistulise adjacent organs [(4,5,6,7)].

Its symptoms include pain, fever, faecal discharge, pus and bleeding and are associated with high morbidity and a very negative impact on the quality of life of patients [(8)].

The treatment of the perianal fistulas is complex, requiring a multidisciplinary approach in which coordination between the surgical team, the clinical team and the radiology service is essential.

The therapeutic approach includes surgical and pharmacological measures. The surgical treatment consists of draining of collections and placing setons (lines), depending on the symptoms and complexity of the fistulas. A fistulectomy or fistulotomy is only performed very selectively, due to the risk of incontinence. Derivative stomata as well as proctectomy may be necessary in severe cases refractory to pharmacological treatment. The pharmacological treatment, on the other hand, includes antibiotics (metronidazole and/or ciprofloxacin), immunosuppressants (azathioprine or mercaptopurine), and/or anti-TNF [(3,9)].

To evaluate the response to pharmacological or surgical treatment in clinical practice, clinical evaluation (absence of drainage and complete closure of the external fistulous orifice) and imaging are recommended. Magnetic resonance imaging (MRI) is the imaging technique of choice to delimit topography, extent, and possible collections [3,10,11].

2. TREATMENT OBJECTIVE

The goal of darvadstrocel treatment in patients with complex perianal fistulas in CD is to achieve fistula remission, defined as complete closure of all external orifices (absence of secretion despite soft finger compression) and absence of collections (greater than 2 cm) confirmed by MRI on the perianal region.

3. PATIENT SELECTION CRITERIA [12, 13]

Patients who meet **all** the following criteria, which must be adequately documented, are considered candidates for initiation for treatment with darvadstrocel:

1) Age equal to 18 years or older and good general state of health.

2) CD diagnosed at least in the previous 6 months according to accepted clinical, endoscopic, histological and/or radiological criteria.

3) Inactive or mild luminal CD, defined by a Crohn's disease activity index (CDAI) of 220 or lower.

4) Draining in the last 6 weeks

5) Complex perianal fistula defined as one that meets one or more of the following requirements:

   - High inter-sphincteric, high trans-sphincteric, extra-sphincteric or supra-sphincteric
   - Presence of 2 or more external orifices
   - Associated collections

6) Presence of two internal and three external orifices maximum.

7) Absence of abscesses or perianal collections of more than 2 cm within at least two diameters, unless these are resolved in preparation.

8) Failure of a full and adequate course of conventional treatment (including antibiotics and immunosuppressive therapy).

9) Failure of anti-TNF treatment for fistulising disease or when there is medical intolerance or contraindications to such treatment.

10) No previous treatment with mesenchymal stem cells.

Compliance with the criteria set out in points 3, 4, 5, 6 and 7 will be justified by performing the following tests:

- Examination (under anaesthesia or sedation in the operating theatre) of the anatomy of the fistula (number of fistulae and existing orifices), its topography (extent and relationship to the sphincters and other pelvic muscles), possible associated complications (such as abscesses) and whether the luminal involvement of the local mucosa is mild or inactive.

  In addition, based on the recommendations of the summary of product characteristics, curettage of all fistula tracts should be performed at this time. If abscesses are present, incision, drainage and placement of setons, if appropriate, is necessary in accordance with standard surgical practice. Before scheduling treatment with darvadstrocel, the absence of abscesses of 2 cm or more must be demonstrated, as this is an exclusion criterion for treatment.

  According to the summary of product characteristics, this should be performed 2-3 weeks before the day of administration (14)

  and

- MRI of the perianal region with intravenous contrast[a]

[a] In patients whose clinical situation prevents this test from being carried out, another imaging test with adequate diagnostic accuracy could be considered to rule out the existence of collections, in accordance with clinical practice guidelines (10,15).

Patients with any of the following clinical conditions are not considered candidates for treatment[b]:

- Rectovaginal fistulas
- Anal or rectal stenosis
- Active severe proctitis, defined as the presence of superficial or deep ulcers (confirmed by rectoscopy).
- Diverting stomas
- Previous active fistula surgery other than abscess drainage and/or seton placement.
- Treatment with systemic corticosteroids in the previous 4 weeks.
- Presence or previous history of any type of carcinoma over a perianal fistula as well as active malignant tumours.
- Congenital or acquired immunodeficiencies.
- Pregnant, breast-feeding or women of childbearing age who are not using an effective method of contraception during treatment with darvadstrocel.
- Patients with severe renal or hepatic impairment.

Treatment with darvadstrocel is contraindicated in cases of hypersensitivity or allergy to human serum albumin (HSA), Dulbecco's Modified Eagle's Medium (DMEM, containing amino acids, vitamins, salts and carbohydrates), bovine serum or other materials of this origin.

Darvadstrocel may contain small amounts of benzylpenicillin and streptomycin, which should be considered in patients with known hypersensitivity to these classes of antibiotics.

[b] Populations excluded from the pivotal clinical trial. No data are available.

4. GENERAL CONSIDERATIONS FOR TREATMENT WITH DARVADSTROCEL

Darvadstrocel should only be administered by specialist physicians experienced in the diagnosis and treatment of complex fistulas, following clinical assessment of the fistula and MRI examination (see Section 3. Patient selection criteria).

Fistular pathways should be conditioned immediately prior to administration of darvadstrocel.

The dosage and administration method described in the authorised summary of product characteristics must be carefully followed[14], as well as all the instructions contained in the training materials for healthcare professionals that form part of the risk management plan for the medicinal product and that are published on the website of the Spanish Agency for Medicines and Medical Devices[16,17,18].

5. EVALUATION AND MONITORING

The doctor responsible for the patient in each of the stages of the process must register the following information in VALTERMED.

<u>General patient details</u> (to be collected in VALTERMED before starting treatment to carry out the evaluation):

- At least one of the following: NHS code, CIP/CITE code, NIF/NIE, health card
- Medical Record No.:
- Sex:
- Date of birth:
- Anthropometric data prior to therapy. Weight (kg): Height (cm):

<u>Disease characterisation at diagnosis of the treatable fistula</u>

- Date of diagnosis of Crohn's disease.
- Crohn's disease activity index (CDAI)
- Type of fistula according to anatomical classification (high inter-sphincteric, high trans-sphincteric, extras-phincteric or supra-sphincteric).

- Number of internal orifices
- Number of external orifices
- Presence of associated collections (the presence of abscesses larger than 2 cm within at least two diameters is a criterion for exclusion from treatment).
- Date of patient examination under anaesthesia for fistula characterisation (2-3 weeks before the day of administration).
- MRI date for fistula characterisation (not more than 4 weeks before administration)
- Date of rectoscopy to rule out the presence of severe active proctitis (not more than 4 weeks before administration).

Previous treatments

- Pharmacological (antibiotics, immunosuppressants and anti TNF)
- Previous surgeries on active fistula

Darvadstrocel administration

- Date admitted to hospital:
- Date of administration:
- Dose administered:
- Number of external and internal orifices treated:
- No administration. Specify reason:

Evaluation at 6 months post-administration of:

The response variable to be assessed is combined remission, which is defined as clinical closure of all treated fistulae (absence of discharge despite gentle finger compression) and absence of abscesses larger than 2 cm confirmed by MRI with intravenous contrast on the perianal region.

- **The following clinical results should be recorded at 6 months** (+/- 15 days) after administration of darvadstrocel, respectively **(required fields):**
  1. Clinical closure of treated fistulas at 6 months

-yes/no

2. Absence of collections (greater than 2 cm within at least two diameters, determined by MRI) at 6 months
   -yes/no

- **Optionally, at 12 months and thereafter at 24 months,** the following data will be recorded:
  1. Clinical closure of treated fistulas
     -maintenance of response at 12 months: yes/no
     -maintenance of response at 24 months: yes/no

  2. Absence of abscesses (greater than 2 cm within at least two diameters, determined by MRI)
     -maintenance of response at 12 months: yes/no
     -maintenance of response at 24 months: yes/no

Safety

Darvadstrocel is a medicinal product subject to additional monitoring. All legal obligations relating to safety monitoring must be followed, including the reporting of suspected adverse reactions through the Spanish Pharmacovigilance System (SEFV): www.notificaram.es Recording adverse reactions in VALTERMED does not exempt from the obligation to report them through the SEFV in accordance with current legislation [19].

For the purposes of this protocol, adverse events potentially related to treatment or the administration procedure will be recorded whenever they are considered relevant. In particular, the following must be recorded:

- Suspected development of new anal fistula and/or anal abscesses or recurrence of treated fistula.
- Those related to the transmission of bacterial, viral or fungal pathogens.
- Other adverse events potentially related to darvadstrocel (specify):

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