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Stem cell transplantation for induction of remission in medically refractory Crohn's disease (Protocol)

El-Nakeep S, Abdel Latif O, Shawky A, Nabhan AF

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[Intervention Protocol]

Stem cell transplantation for induction of remission in medically refractory Crohn's disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objective of this review is to assess the efficacy and safety of stem cell transplantation for induction of remission in active Crohn's disease.

BACKGROUND

Description of the condition

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that typically affects young adults between 15 and 35 years of age. The prevalence of Crohn's disease is nearly 320 per 100,000, with the highest prevalence in Europe and North America. The prevalence of Crohn's disease in developing countries might be underestimated due to a lack of rigorous population-screening studies (Molodecky 2012).

Crohn's disease presents mainly with abdominal pain, diarrhoea, fever, malabsorption, and weight loss (Abraham 2009; Ruiz 2015). Crohn's disease causes both mucosal and transmural inflammation that can affect any part of the gastrointestinal tract, but mostly the small bowel (Wiarda 2012). There are three Crohn's disease behaviours (Montreal classification) that can occur at any time during the disease course. These are non-stricturing non-penetrating, stricturing and penetrating disease (Satsangi 2006). Common complications of Crohn's disease include perianal fistulae and abscesses. Some patients may have immune-mediated extra-intestinal (i.e. arthritis, eye, skin, and liver) manifestations (Isene 2015; Peyrin-Biroulet 2017).

Crohn's disease follows a relapsing and remitting course (Nikfar 2013). The therapeutic goal of treatment is to induce and maintain clinical remission. Different interventions have been investigated for inducing remission in active Crohn's disease (Dassopoulos 2013). These interventions include systemic corticosteroids such as hydrocortisone or prednisolone (Benchimol 2008), locally acting corticosteroids such as budesonide (Rezaie 2015), sulphasalazine (Lim 2016), tumour necrosis factor alpha (TNF-α) antagonists such as infliximab (Kawalec 2013), azathioprine (Chande 2016), interleukin inhibitors e.g. ustekinumab (MacDonald 2016), methotrexate (McDonald 2014) and alpha-4 integrin monoclonal antibodies such as vedolizumab (Sandborn

2013).

Immunosuppressive drugs are the standard treatment for Crohn's disease. For those who do not respond, or lose response to this therapy, treatment solutions become a challenge (Cooper 2017). Further, endoscopic recurrence following surgery may occur in up to 70% of cases (Day 2013; Lawrance 2014).

Description of the intervention

Stem cell therapy includes hematopoietic stem cells (HSCs) and mesenchymal stem (stromal) cells (MSCs). Stem cell therapy, whether HSCs or MSCs, can be subdivided into autologous donation (isolated from the patient) or allogenic donation (isolated from a donor, ideally human leukocyte antigen matched) (Dalal 2012; Duran 2016).

HSCs can be isolated from bone marrow, umbilical cord blood, or more commonly peripheral blood. HSCs are progenitors of both myeloid (monocytes, erythrocytes macrophages, neutrophils, and dendritic cells) and lymphoid (T cells, B cells, and natural killer cells) lineages. HSCs can be administered by an intra-arterial or intravenous approach (Duran 2016). MSCs can be successfully isolated for clinical application from bone marrow, umbilical cord blood or adipose tissue. MSCs can be administered by an intra-arterial or intravenous route or by local injection (Duran 2016).

How the intervention might work

The goal in treating CD is to achieve remission and halt any ongoing disease progression (Gomollón 2017). Stem cells have immunoregulatory potential. Therefore, stem cell therapy, either hematopoietic or mesenchymal, may induce remission in active CD (Dalal 2012; Dave 2015; Duran 2016; Ricart 2013).

HSCs extends immune modulation and suppression by maximizing immune suppression to the point of immune ablation. HSCs can migrate to a damaged tissue or differentiate to epithelial or immunomodulatory cells in order to restore normal mucosal tissue (Duran 2016). The role of HSCs in treating inflammatory bowel disease was originally supported by clinical remissions observed in patients undergoing stem cell transplant for haematological disorders. These observations led to trials of HSCs in patients with active Crohn's disease (Burt 2003; Burt 2010; Cassinotti 2008; Clerici 2011; Craig 2003; Kreisel 2003; Oyama 2005). The largest multi-centre randomised clinical trial of autologous HSCs in refractory CD was conducted from 2007 to 2011, with follow-up through 2013 (Hawkey 2015). The infusion of either autologous or allogeneic HSCs is associated with adverse events, with cardiovascular and pulmonary adverse events being the common (Vidula 2015).

MSCs are multipotent cells that have immunomodulating capabilities to down-regulate mucosal immune reactivity and promote tissue healing. MSCs can inhibit T-cell proliferation in vitro, and can inhibit lymphocyte proliferation by activating a programmed cell death pathway. There are only a few studies reporting on the use of autologous (Duijvestein 2010), or allogeneic (Forbes 2014), bone marrow-derived MSCs for luminal Crohn's disease. In fistulising CD, local injection of MSCs may be beneficial for healing of the fistula (Ciccocioppo 2011; de la Portilla 2013; Garcia-Olmo 2005; Garcia-Olmo 2009; García-Arranz 2016; Lee 2013).

Why it is important to do this review

Patients with active CD suffer high morbidity and mortality. Controversy regarding the potential benefits and harms of stem cell transplant for patients with active Crohn's disease still exists (Duran 2016; Gomollón 2017). This systematic review summarizes the current evidence regarding the efficacy and safety of stem cell transplantation in active Crohn's disease.

OBJECTIVES

The objective of this review is to assess the efficacy and safety of stem cell transplantation for induction of remission in active Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised and quasi-randomised trials that assessed the efficacy and safety of stem cell transplantation compared to placebo or other active treatments used for induction of remission in Crohn's disease.

Types of participants

We will include participants with active Crohn's disease as defined by conventional clinical, radiological or endoscopic criteria. We will not restrict inclusion by age or gender.

Types of interventions

Interventions that involved the administration of different types of stem cells will be considered for inclusion.

We will include the following comparisons:

1. HSCs transplantation versus placebo or other active treatments;

2. MSCs transplantation versus placebo or other active treatments; and
3. Local MSCs injection versus placebo or other active treatments.

Types of outcome measures

Primary outcomes

The primary outcomes will include:
1. Clinical remission, as defined by the original studies (e.g. a Crohn's Disease Activity Index (CDAI) of ¡ 150) or a Pediatric Crohn's Disease Activity Index (PCDAI) of ¡ 15 at weeks 4 to 6 (early), weeks 10 to 12 (middle), and weeks 15 or later (late) following initiation of therapy; and
2. Complete closure of the fistula as defined by th original studies (e.g. complete closure of the fistula tract including internal and external openings without drainage or any sign of inflammation either detected; assessed clinically or by magnetic resonance imaging or Perianal Disease Activity Index score).

Secondary outcomes

Secondary outcomes will include:
1. Clinical improvement, as defined by the original studies;
2. Endoscopic remission, as defined by the original studies (e.g. Crohn's disease endoscopic index of severity [CDEIS], Simple endoscopic score for Crohn's disease [SES-CD], Rutgeerts' Post-operative endoscopic index);
3. Endoscopic improvement, as defined by the original studies;
4. Adverse events (e.g. perianal abscess, bacterial gastroenteritis);
5. Serious adverse events (e.g. sepsis, graft versus host disease);
6. Withdrawals due to adverse events;
7. All cause mortality; and
8. Quality of life as defined by the original studies (e.g. Inflammatory Bowel Disease Questionnaire [IBDQ]) or Short Form Health Survey SF-36, IBD-Control 8, Crohn's Ulcerative Colitis Questionnaire-8 [CUCQ-8] or IMACT III for paediatric patients).

Search methods for identification of studies

Electronic searches

To identify relevant studies, we will search the following databases from inception to date:
1. MEDLINE (1966 to date);
2. Embase (1980 to date);
3. CENTRAL; and
4. Cochrane IBD Group Specialized Register from inception to date to identify relevant publications.

The search strategies are reported in Appendix 1. No language restrictions will be applied.

Searching other resources

We will search the following databases for ongoing trials:
- US National Institutes of Health Trials Registry (clinicaltrials.gov); and
- The World Health Organization (WHO) Clinical Trials Registry Platform (apps.who.int/trialsearch/default.aspx).

Checking reference lists

We will hand search reference lists of all included primary studies and relevant review articles for additional studies.
We will perform a manual review of available bibliographies and abstracts submitted to major gastroenterology meetings (inception to present) including:
1. Digestive Disease Week;
2. American College of Gastroenterology;
3. Crohn's and Colitis Foundation of America;
4. United European Gastroenterology Week; and
5. European Crohn's and Colitis Organization.

Data collection and analysis

We will use the standard methodological procedures expected by Cochrane for the conduct and reporting of this systematic (Higgins 2016).

Selection of studies

Two authors (SEN and OAL) will independently review the titles and abstracts of the studies identified from the literature search. The full text of potentially relevant citations will be reviewed for inclusion. Any disagreements will be resolved by discussion and consensus with a third author as necessary (AFN). We will not include trials presented as abstracts. We will create a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We will design a data extraction form to extract data. For eligible studies, two review authors (SEN and OAL) will independently extract the data. We will resolve discrepancies through discussion and consensus or, if required, we will consult a third author (AFN). We will enter data into Review Manager software (RevMan 2014). Extracted data will include the following items:

1. Characteristics of patients: age, sex, disease duration, disease location, type of Crohn's disease activity index used;
2. Total number of patients in each study and in each group;
3. Previous and concomitant medications used;
4. Outcomes: clinical remission, quality of life, mortality, adverse effects;
5. Type of intervention: HSCs or MSCs;
6. Type of stem cells used: autologous or allogeneic;
7. Route of administration: systemic or local;
8. Mode and source of collection of the cells: direct marrow biopsy, cell mobilization from the marrow, somatic cells reprogrammed, umbilical cord, adipose tissue;
9. Type of reconditioning used in cell collection if present; and
10. Disease behavior (inflammatory, fibrostenosing, penetrating).

Assessment of risk of bias in included studies

Two review authors (SEN and OAL) will independently assess the risk of bias for each study using the Cochrane risk of bias tool (Higgins 2011). Detailed methods for the risk of bias assessment are shown in Appendix 2. We will resolve any disagreement by discussion or by involving a third assessor (AFN).
We will assess the following items:
1. Random sequence generation (checking for possible selection bias);
2. Allocation concealment (checking for possible selection bias);
3. Blinding of participants and personnel (checking for possible performance bias);
4. Blinding of outcome assessment (checking for possible detection bias);
5. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data);
6. Selective reporting (checking for reporting bias); and
7. Other bias (checking for bias due to problems not covered by items above).

For each item we will make explicit judgments about high, low or unclear risk of bias. Overall, we will make explicit judgments about whether studies are at high, low or unclear risk of bias. With reference to (1) to (7) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias by conducting sensitivity analysis (see Sensitivity analysis).

GRADE and 'Summary of findings' table

We will use the GRADE approach (Schünemann 2009), to create a 'Summary of findings' table for the following main outcomes.
1. Clinical remission;
2. Fistula closure;
3. Clinical improvement;
4. Adverse events;
5. Serious adverse events; and
6. Withdrawals due to adverse events

GRADEpro GDT will be used to import data from Review Manager 5.3 (RevMan 2014), in order to create the 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome. Evidence from randomised trials starts as 'high quality', The evidence is downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on the assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates and potential publication bias.

Measures of treatment effect

All data will be analysed on an intention-to-treat (ITT) basis using Review Manager (RevMan 5.3.5). We will calculate the risk ratio (RR) and corresponding 95% confidence interval (CI) for dichotomous outcomes. For continuous outcomes, we will calculate the mean difference (MD) and corresponding 95% CI.

Unit of analysis issues

When studies report multiple observations for the same outcome, we will combine outcomes for fixed intervals of follow-up (e.g. clinical remission at eight weeks). We will include cross-over trials if data are available from the first phase of the study (i.e. before cross-over). Separate comparisons will be conducted for stem cell therapy versus placebo and stem cell therapy versus active comparator. If studies allocate participants to more than one stem cell treatment arm, these studies will be pooled for the primary analysis.

Dealing with missing data

The primary analysis will be an ITT analysis. We will contact the trialists to request missing data, or to ascertain the reason for data loss. Otherwise, missing dichotomous data will be assumed to be treatment failure. The impact of this assumption on the effect estimate will be assessed by performing sensitivity analyses where appropriate. We will conduct an available case analysis for continuous outcomes with missing data.

Assessment of heterogeneity

We will assess statistical heterogeneity for each pooled analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if I^2 is greater than 50% and either Tau^2 is greater

than one, or the P value for the Chi^2 test is statistically significant (i.e. less than 0.10).

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate potential explanations.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will combine data from individual trials for meta-analysis when the interventions, patient groups and outcomes are sufficiently similar (as determined by consensus). For dichotomous outcomes, the pooled RR and 95% CI will be calculated. For continuous outcomes, the pooled MD and corresponding 95% CI will be calculated. When different scales are used to measure the same underlying construct (e.g. different quality of life instruments), we will calculate the standardized mean difference (SMD) and 95% CI. A fixed-effect model will be used to pool data unless heterogeneity exists between the studies. If heterogeneity exists (I^2 = 50% to 75%), a random-effects model will be employed. If a high degree of heterogeneity is detected ($I^2 \geq$ 75), we will not pool data for meta-analysis.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity (I^2 statistic $\geq$ 50% or P ¡ 0.1), we will investigate it using subgroup analyses and sensitivity analyses.

We will restrict subgroup analyses to the primary outcome. We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

If there are sufficient data, the following subgroup analyses will be conducted:

1. Autologous versus allogeneic stem cells;
2. High dose versus low dose stem cells;
3. Paediatric versus adult participants;
4. Male versus female participants; and
5. Treatment after recurrence versus treatment naive participants.

Sensitivity analysis

We plan to carry out a sensitivity analysis to explore: .

1. Random-effects versus fixed-effect modelling;
2. Low risk of bias versus 'high risk of bias' and 'unclear risk of bias' when considering allocation concealment and incomplete outcome data.

We plan to restrict the sensitivity analyses to the primary outcome.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search Strategy

MEDLINE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. randomized controlled trial/
14. or/1-13
15. Exp Crohn disease/
16. Crohn*.mp.
17. IBD.mp.
18. Inflammatory bowel disease*.mp.
19. Or/15-18
20. Exp Stem cell transplant/
21. Stem cell*.mp.
22. Stem cell therap*.mp.
23. SCT.mp.
24. Mesenchymal stem cell*.mp.
25. Hematopoietic stem cell*.mp.
26. Autologous hematopoietic.mp.
27. HPSC.mp.
28. Bone marrow transplant*.mp.
29. BMT.mp.
30. Autologous bone marrow.mp.
31. Autologous stem cell*.mp
32. CD34+ cell*.mp
33. Pluripotent stem cell*.mp.
34. Adult stem cell
35. Or/20-34
36. 14 and 19 and 35

Embase

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. Exp Crohn disease/
20. Crohn*.mp.
21. IBD.mp.
22. Inflammatory bowel disease*.mp.
23. Or/19-22
24. Exp Stem cell transplant/
25. Stem cell*.mp.
26. Stem cell therap*.mp.
27. SCT.mp.
28. Mesenchymal stem cell*.mp.
29. Hematopoietic stem cell*.mp.
30. Autologous hematopoietic.mp.
31. HPSC.mp.
32. Bone marrow transplant*.mp.
33. BMT.mp.
34. Autologous bone marrow.mp.
35. Autologous stem cell*.mp
36. CD34+ cell*.mp
37. Pluripotent stem cell*.mp.
38. Adult stem cell
39. Or/24-38
40. 18 and 23 and 39

CENTRAL

#1 MeSH: [Inflammatory bowel disease] explode all trees
#2 MeSH: [Crohn Disease] explode all trees
#3 Crohn
#4 IBD
#5 #1 or #2 or #3 or #4
#6 MeSH: [Stem Cell] explode all trees
#7 MeSH: [Marrow transplantation] explode all trees
#8 MeSH: [Hematopoietic stem cell] explode all trees
#9 MeSH: [Stem cell therapy] explode all trees
#10 #6 or #7 or #8 or #9
#11 #5 and #10

Select "trials only"

Appendix 2. Risk of bias assessment

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess random sequence generation as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess allocation concealment as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk of bias.

(3) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess blinding of participants and personnel as:

- low, high or unclear risk of bias for participants; and
- low, high or unclear risk of bias for personnel.

(4) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(5) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will include missing data in the analyses which we undertake.
We will assess incomplete outcome data as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation); or
- unclear risk of bias.

(6) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where a protocol exists and it is clear that all pre-specified outcomes are reported and where a protocol doesn't exist and all expected outcomes have been reported);
- high risk of bias (where a protocol exists and not all of the pre-specified outcomes have been reported; where a protocol doesn't exist and an expected outcome is reported incompletely or the study fails to report key outcomes that would have been expected to have been reported); or
- unclear risk of bias.

(7) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias; or
- unclear whether there is risk of other bias.

CONTRIBUTIONS OF AUTHORS

Dr. Sarah El-Nakeep: writing of the protocol.

Dr. Ossama Abdel Latif: writing of the protocol.

Prof. Ashraf Nabhan: revision of the protocol and providing expert methodological opinion.

Prof. Ahmed Shawky: revision of the protocol and providing the expert clinical opinion.

DECLARATIONS OF INTEREST

Sarah El Nakeep: None known

Osama Abdel Latif: None known

Ahmed Shawky: None known

Ashraf F Nabhan: None known

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