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**One more chance of fistula healing in inflammatory bowel disease: Stem cell therapy**

Turse EP *et al*. Stem cell therapy for fistula in CD

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**Abstract**

Patients with fistulizing inflammatory bowel disease are traditionally difficult-to-treat. This patient population often experiences delayed or insufficient healing of fistulas using current standard regimens including antibiotics, immunomodulators, anti-tumor necrosis factor-α drug, placement of setons, and surgical repair. Several studies over the last ten to fifteen years have been conducted using stem cell therapies with promising results in this patient population, which are reviewed below. These studies show stem cell therapy in fistulizing disease to be successful in healing between 60%-88% compared to currently 50% with infliximab. Moreover, remission was seen 24 wk to 52 wk in these studies. Further research with a multi-approach treatment using medications, stem cell therapy, and surgical interventions will likely be the future of this innovative treatment approach.

**Key words:** Inflammatory bowel disease; Crohn’s disease; Stem cells; Mesenchymal; Fistulizing; Fistula

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**Core tip**: There appear to be limited adverse events as well as significant benefit to multi-approach therapy using stem cells to treat fistulizing inflammatory bowel disease. Comparing studies to current treatment rates of fistula healing, which has a less than 50% success rate, stem cell therapy for fistulizing Crohn’s disease appears to be beneficial, as the majority of studies claim 60%-88% fistula healing and maintenance of remission at 24-52 wk. Further large-scale studies analyzing a multi-approach therapy including stem cells should be conducted, especially in a randomized double-blind approach.

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**INTRODUCTION**

Inflammatory bowel disease (IBD), including Crohn’s disease (CD), ulcerative colitis (UC), and IBD-unclassified, is a very complicated unique spectrum of disease processes, ranging from relatively asymptomatic to daily complications of significant pain and fistulizing disease. While fistulizing disease primarily occurs in CD, sometimes patients are initially diagnosed with UC, which later is realized to actually be CD. Furthermore, UC patients sometimes develop fistulas for other reasons besides their IBD. Unfortunately, little is known on which afflicted individuals will progress despite signs and symptoms, with approximately 25% of CD patients developing fistulas within 20 years of diagnosis[1]. Some patients will do well and achieve complete remission with newer biological agents (*i.e.* vedolizumab) and placement of setons, while others will continue to be refractory in their disease course. Antibiotics, immunomodulators, and anti-tumor necrosis factor-alpha (TNF-α) drugs all have been utilized for fistulizing disease with less than ideal response rates: 90% recurrence with antibiotics and 50% recurrence with infliximab[2]. Furthermore, one-third of patients do not respond to anti-TNF-α medications and 10% of patients are non-responders to existing medications[3]. Stem cell therapy has emerged as treatment for these difficult-to-treat patients with fistulizing CD. In this review, the authors aim to highlight the progression of stem cell therapies in patients with refractory CD with fistulizing disease. A literature search of clinical trials in humans was performed with PubMed through April 2018 using keywords including stem cell therapy, fistulas, fistulizing, IBD and CD. The searches were limited to English language, and excluded comments, editorials, or letters. The outcomes of safety and efficacy using this innovative treatment are presented throughout and are outlined after each section of type of stem cell modality in Tables 1-5.

Four main groups of stem cell therapies exist which include embryonic, tissue-specific, mesenchymal and induced pluripotent stem cells. Most studies evaluating treatment of fistulizing disease for IBD patients utilize mesenchymal stem cell (MSC) therapy, whether autologous or allogeneic in nature. MSC are stromal cells surrounding other tissues and organs that are able to undergo angiogenesis of the cells they are derived from and are available to help with immunomodulatory effects; this includes adipose tissue and bone marrow cells. Three criteria for MSC *in vitro* must be met *per* the International Society for Cellular Therapy, which include differentiation potential *i.e.* adipogenic lineages, expression of surface antigens including human leukocyte antigen DR-, CD79a, CD19-, CD14-, CD11b-, CD45-, CD34-, CD105+, CD90+, CD73+, and ability to adhere to plastic[4]. Limited studies exist in animal models and human trials, yet there has been an emergence of research in this area within the last ten years. The majority of these studies had the same exclusion criteria unless otherwise specified below. These included evidence of any infections, the need for antibiotics or immediate surgery, unwilling to use contraceptives, pregnant or breast-feeding, presence of complex fistulas with more than 2 openings or malignancy within the past five years, and any evidence of end-organ failure. Fistulas in most studies were a mix of transsphincteric, suprasphincteric, and extrasphincteric and sometimes rectovaginal. No studies using stem cell therapy specifically for fistulizing disease commented on development of graft versus host disease. Most side effects were limited for stem cell therapy with fistulizing disease as local injection was used. However, with hematological stem cell therapy infusions the most common adverse effect seen was systemic infection.

**AUTOLOGOUS ADIPOSE TISSUE DERIVED STEM CELL THERAPY TRIALS**

Autologous adipose tissue derived stem cell (ASC) therapy is a type of MSC therapy derived from one’s own adipose tissue. In 2003, one of the first case reports for fistulizing CD using ASC for CD-related rectovaginal fistulas (CRRVF) was reported[5]. This utilized ASC for a patient with refractory disease to infliximab and placement of setons, with resultant resolution of symptoms in one week after local injection with no reoccurrence after three months.

Lee *et al*[6] studied 33 patients with fistulizing disease using autologous ASC proportional to fistula surface area by conducting a non-randomized, single group assignment open-label phase 1 study. Using photography, patients were documented on weeks 4, 6, and 8 and if complete healing was not found at week 8, re-injected with ASC. The authors defined complete healing as “complete closure of fistula tract and internal and external openings, without drainage or any sign of inflammation”[6]. Here, promising results of ASC therapy for fistulizing disease were seen with 79% of patients showing complete closure after a first dose, and 88.5% of patients not having recurrence at the one-year mark. This study had a wide variety of patients regarding their duration of CD and duration of fistula.

Next, Cho *et al*[7] studied autologous ASC in a phase 1 non-randomized, open-label dose escalation trial with 10 patients enrolled. Three dosing groups with three patients in each were evaluated with dosing given at four-week intervals and patients evaluated at 8 wk, and 4, 6, and 8 mo. Fifty percent of patients after a single injection observed complete healing, compared to 16% with prior studies of fibrin glue. These patients who showed healing at 8 wk sustained healing at 8 mo. The authors compared this to a fistula recurrence rate of 43% of patients with CD treated with infliximab[7].

In addition, Cho *et al*[8] went on to analyze 41 of 43 patients in their previous phase 2 trial with dosage proportional autologous ASC administration for an additional year in a retrospective chart review of these patients. They evaluated sustainability and efficacy of ASC applied and further documented safety 24 mo after ASC administration. Patients were excluded if they had operations during that timeframe and three patients met this criterion; four patients were excluded due to lack of data. Results showed 82% of patients had resolution of their fistulas and durability was 80% (*P* ≤ 0.0001) at 12 mo and 75% (*P* ≤ 0.001) at 24 mo.

Furthering stem cell therapy studies, Dietz *et al*[9] conducted a phase 1 single center non-randomized trial evaluating stem cell treatment for patients remaining on biologic therapy of infliximab, adalimumab, and certolizumab. Twelve patients were given a stem cell loaded plug (MSC-MATRIX) with complete clinical healing in 75% of the population at 3 mo, and 83.3% within 6 mo. MRI was used to define characteristics of treated fistula tracts at baseline and six months to further confirm healing.

**AUTOLOGOUS BONE MARROW DERIVED STEM CELL THERAPY TRIALS**

Between 2007 and 2014, Ciccocioppo *et al*[10] looked at fistulizing CD assessing patients with autologous bone marrow-derived MSC (BM-MSC) for safety and efficacy. The authors found that fistula relapse-free survival was 88%, 50% and 37% at 1, 2 and 5-year follow-up with no adverse events (AE). Thus, they concluded that BM-MSC was safe and efficacious for fistulizing CD.

**ALLOGENEIC ADIPOSE TISSUE DERIVED STEM CELL THERAPY TRIALS**

García-Arranz *et al*[11] conducted a phase 1-2 non-randomized, open-label trial with 10 patients using allogeneic ASC for rectovaginal fistulas. Primary endpoint was safety and feasibility to treat CRRVF and patients were followed at 1, 4, 8, 12, 24, and 52 wk after ASC administration. If complete re-epithelialization was not obtained by week 12, a second dose of ASC was administered. CRRVF was defined as healed “when the vaginal and rectal walls showed complete re-epithelialization and absence of vaginal drainage, including feces, flatus or suppuration”. Nine patients had their fistula cured during the study, yet fistula reoccurrence occurred in seven of these patients. Due to patients being excluded for reasons such as need for biologic therapy or surgeries, the final efficacy rate for sustained fistula healing at 52 wk was 60% (three of five patients did not have reoccurrence). It was concluded that the primary endpoint was met as the study was found to be safe and feasible as a treatment option.

de la Portilla *et al*[12] analyzed in a phase 1-2 open-label single-arm non-randomized multi-center study 24 patients, who were given allogeneic expanded adipose-derived ASC (eASC) for complex perianal fistulas in CD. The endpoint was to determine safety and efficacy in this population. Patients underwent initial magnetic resonance imaging (MRI) and then eASC injection with a second injection if incomplete closure was found at 12 wk, with conclusion of the study at 24 wk. The same definition of closure as the Lee *et al*[6] study was used with evaluation at weeks 10, 12, 22, and 24 by both the treating physician and a blinded gastroenterologist/surgeon. The study found that 69.2% patients had reduction in their fistula, with 38.1% patients achieving complete closure at week 12 and 65.3% at week 24. Thus, it was concluded that eASC were safe and efficacious in treatment of complex perianal fistulas.

Panés *et al*[13] authored a phase 3 randomized, double-blind, parallel-group, placebo-controlled, multi-center trial utilizing eASC as treatment in complex perianal fistula CD patients known as the ADMIRE CD study. Patients with stenosis, CRRVF, diverting stoma, or abscesses > 2 cm were additionally excluded to the above criteria. Inclusion criteria for the study were patients with refractory disease to immunologic, antibiotics, or biologics such as anti-TNF drugs. Closure was a similar definition as the above studies. Two hundred and twelve patients were randomly assigned, with 88 *vs* 83 patients at completion of the 24 wk. Overall, 50% of patients treated with eASC either solo or in combination with medical treatment achieved remission compared to 34% in the placebo group (*P* = 0.024)[13]. Treatment was also documented to be safe and efficacious with similar adverse reactions occurring more in the placebo group, thus being secondary to the nature of disease course in CD.

Published recently, Panés *et al*[14] extended the ADMIRE CD Study from 24 wk to 52 wk documenting both clinical remission and combined remission. They defined this as “clinical assessment of closure of all treated external openings that were draining at baseline and the absence of collections > 2 cm”. The trial concluded that eASC is still superior to placebo with clinical remission in 59.2% Cx601 *vs* 41.6% placebo (95%CI: 4.1-31.1; *P* = 0.013) and 56.3% *vs* 38.6% (95%CI: 4.2-31.2; *P* = 0.010) in combined remission.

Wainstein *et al*[15] also published a single center prospective observational pilot study conducted during 2013-2016 including nine patients. Two stages were included in this study which was (1) “examination under anesthesia, fistula mapping, drainage and seton placement” and (2) setons removed four to six weeks with subsequent debridement and ASC then injected with biological plug formation. There were three classes of treatment results: complete healing, partial healing, and no healing. Partial healing was defined as external fistula opening remaining but with decrease of > 50% in size. This study found complete healing in 10/11 patients’ fistulas and 1/11 partial healing[15]. Conclusions were made that excellent success rates can be made for fistulizing CD with a multi-approach treatment method including ASCs, platelet rich plasma and endorectal advancement flaps.

**ALLOGENEIC BONE MARROW DERIVED STEM CELL THERAPY TRIALS**

Molendijk’s team conducted a randomized, double-blind, placebo-controlled, dose-escalating study using allogeneic bone-marrow MSCs with surgical treatment for 21 patients with refractory perianal fistulizing CD[1]. The study used either MSCs from five different donors or normal saline-5% albumin solution as placebo with surgery performed by two surgeons with expertise in IBD. Fistula healing was documented by photography at week 0, 12 and 24, in addition to finger pressure at external openings and MRI at week 12. Endpoints were absence of discharge and absence of collections of > 2 cm on MRI. Results were 66.7%, 85.7%, and 28.6% fistula healing for the three groups at week 24 compared to placebo 33.3% (*P* = 0.06 group 2 *vs* placebo)[1] The study concluded that allogeneic bone-marrow MSCs is superior in treating fistula healing than placebo for patients with refractory perianal fistulizing CD.

**MIXED STEM CELL TREATMENT MODALITIES**

Interestingly, there was a case study published in 2015 that included five pregnant females with fistulizing CD analyzing their reproductive outcomes[16]. Of this patient population, three had CRRVF and two had perianal fistulas and had undergone ASC injection with resolution of their fistulas and subsequent ability for pregnancy (between 17 mo to 2 years). Thus, three patients received autologous and two patients had received allogeneic ASC prior to conception with all five patients in their 30 s during administration of ASC, and mid-thirties to early forties for age at gestation[16]. All but one patient had 18-24 mo between ASC and gestation. After their pregnancies, the patients were given data collection sheets. Two of the five patients experienced gestational complications, namely being first trimester miscarriages (no treatment during pregnancy) and fetal growth restriction and small for gestational age (azathioprine during pregnancy). Of the patients who gave birth, all four patients underwent cesarean section with only one newborn malformation occurring, which was syndactyly with clinodactyly[16].

**DISCUSSION**

***Suggestions and Practical Guidance***

Patients who present with continued fistulas from their IBD despite other medical and surgical therapies should be referred to centers that are utilizing stem cell therapies. Such patients can have relief and resolution of anxiety and frustration of their disease process with this novel treatment. Physicians caring for this patient population who consider such therapies should make sure to counsel patients on the risks versus benefits including the commonly seen AE and SAE mentioned above. Additionally, patients should know that if they undergo allogeneic transplantation they may fail to harvest enough stem cells for treatment. Yet, the authors of this paper and the authors of the literature reviewed here are excited for future studies and a novel treatment for a complicated disease.

**CONCLUSION**

In this review, we highlight the progression of utilization of stem cell therapy in fistulizing IBD, specifically CD. While still early along in this evaluation process, these therapies do offer a lot of potential for a difficult-to-treat population. Likely because of its immunomodulatory ability with differentiation and suppression of proliferation, stem cell therapies appear to be a promising treatment option for a sizeable population of CD patients with fistulizing disease.

**FUTURE PERSPECTIVES**

Currently on the horizon, there are four clinical trials registered for fistulizing CD. Three of these studies are recruiting and one is still pending recruitment. Three of these will be non-randomized, one of these will be randomized single-blind, and the majority will be utilizing autologous stem cells[17]. Studies need to be streamlined in the amount of stem cells used and the type of cells harvested such as allogeneic versus autologous hosts and bone marrow versus adipose tissue. Since there does not appear to be a benefit to bone marrow harvesting thus far, we believe that studies should focus on adipose-derived stem cells, either autologous or allogeneic. Comparing studies to current treatment rates of fistula healing, which is less than 50%, stem cell therapy for fistulizing CD appears to be beneficial as the majority of studies claim 60%-88% fistula healing and remission observed at 24-52 wk. Studies even showed benefit of remission 5 years out from administration[10). Moreover, these studies show that stem cell treatment for fistulizing disease is safe with very few AE or significant adverse events (SAE), with the majority including pain, bleeding, or abscesses. Most AE or SAE observed were due to the underlying nature of IBD itself.

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**Table 1 Composite of autologous adipose tissue derived stem cell therapy trials.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Yr of Study** | **Fistula site** | **Type of Study** | **Study population** | **Method of Administration** | **Healing Type of Fistula** | **Safety** | **Outcome** |
| García-Olmo *et al*[5] | 2003 | -RV | Case Report | 1 | Injection of cells into rectal mucosa. | Fully healed | No AE or SAE | Complete resolution at 1 wk with closure still at 3 mo |
| Lee *et al*[6] | 2013 | -TS  -SS  -IS  -ES | Clinical Trial, Phase II Multi-center | 33 | Fistula tract was curetted and irrigated and then ASCs were injected into the submucosa of tract and opening. | 27 of 33 patients with complete fistula healing at 8 wk.  1 of 7 without complete healing had healing after 2nd dose  5 of 33 patients with > 50% closure | -60% postoperative pain  -19% anal pain -7% anal bleeding  -1 patient with exacerbation of disease  -1 patient with peritonitis from enteritis from CD | 79% patients with complete closure after first dose |
| Cho *et al*[7] | 2013 | -TS  -SS  -ES | Clinical Trial, Phase I  Multi-center | 10 | Tract curettage was performed and internal opening was closed. Then, subcutaneous adipose tissue collected by liposuction was injected into the fistula tract wall and the surrounding internal opening. | Group 1: Three patients with partial closure  Group 2: Two patients with complete healing  Group 3: One patient with complete healing, one with partial healing | -13 AE in 7 patients which were not related to study drug: pain, diarrhea  -2 patients SAE: enterocolitis, infliximab administration for new fistulas unrelated to target fistula | All patients with complete closure at 8 wk had sustained complete healing at 8 mo  50% patients after single injection with complete healing. |
| Cho *et al*[8] | 2015 | -TS  -SS  -ES | Clinical Trial, Phase II  Multi-center | 43 | Tract curettage was performed and internal opening was closed. Then, subcutaneous adipose tissue collected by liposuction was injected into the fistula tract wall and the surrounding internal opening. This was done on a primary endpoint of 8 wk; then a retrospective clinical study was conducted looking at patient outcomes after 2 yr. | 41 of 43 patients were enrolled in the retrospective clinical study  After excluded patient: 27 of 33 patients with complete closure | -53 AE in 30 patients: abdominal pain (17.1%), eczema (9.8%) exacerbation of disease (9.8%), anal inflammation (7.3%), diarrhea (7.3%), fever (7.3%) | At 12 and 24 mo, respectively, 80% (*P* ≤ 0.0001) and 75% (*P* ≤ 0.001) of patients continued to have complete closure |
| Dietz *et al*[9] | 2017 | -TS  -SS  -IS | Clinical Trial, Phase I  Multi-center | 12 | Delivered ASC to the fistula through attachment of bioabsorbable matrix for surgical placement (MSC-MATRIX) through intraoperative placement. | 9 of 12 patients with complete healing at 3 mo  10 of 12 patients with compete healing at 6 mo | -1 SAE from CD not study (debridement of granulation tissue of fistula tract)  -2 AE: seromas at site of fat collection  -11 AE: due to underlying CD | 83.3% patients at 6 mo with complete healing after MSC-MATRIX placed |

**Table 2 Composite of autologous bone marrow derived stem cell therapy trials.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Yr of Study** | **Fistula site** | **Study population** | **Method of Administration** | **Healing Type of Fistula** | **Safety** | **Outcome** |
| Ciccocioppo *et al*[10] | 2015 | -Perianal  -Enterocutaneous | 10 | Serial intrafistula injections of autologous bone marrow MSCs. | 2 patients with no recurrence of fistula at 5 yr | No adverse events | Fistula relapse free: 88% at 1 yr, 50% at 2 yr, and 37% during the following 4 yr |

MSC: Mesenchymal stem cell.

**Table 3 Composite of allogeneic adipose tissue derived stem cell therapy trials.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Yr of Study** | **Fistula site** | **Study population** | **Method of Administration** | **Healing Type of Fistula (unhealed, partially, fully)** | **Safety** | **Outcome** |
| García-Arranz *et al*[11] | 2016 | -RV | 10 | Tract curettage was performed and vaginal or rectal flap added with intralesional injection of 20 million allogeneic adipose stem cells injected into the fistula tract and vaginal submucosa. If complete healing was not seen at 12 wk, patients were re-administered stem cells. | 2 patients with complete healing at 12 wk  2 patients with complete healing from the 8 patients with second administration of stem cells.  9 patients at some point during the study had fistula healing | No SAE or AE | 3 of 5 patients included in total (others excluded during study) remained healed at 52 wk, showing 60% efficacy |
| de la Portilla *et al*[12] | 2013 | -Perianal | 24 | Intralesional fistula tract injection with stem cells with repeat administration at 12 wk with dose escalation if incomplete closure. | 38.1% patients achieved complete closure at week 12  65.3% patients achieved complete closure at week 24 | 13 patients with 32 AE and of these 5 were treatment related: anal abscess (3 patients), pyrexia (1 patient), uterine leiomyoma (1 patient) | 69.2% patients had fistula reduction at 24 wk |
| Panés *et al*[13] | 2016 | -TS  -SS  -IS  -ES | 212 | Patient randomized into two groups:  -Placebo with 24 ml saline  -Intralesional injection of Cx601 cells  Study conducted over 24 wk | 50% patients with Cx601 *vs* 34% placebo achieved complete fistula healing and remained closed at week 24 (*P* = 0.024) | TEAE: proctalgia, anal abscess, and nasopharyngitis.  5% in treatment group and 6% in placebo group withdrew. | Cx601 is effective and safe for treatment of refractory fistulizing CD |
| Panés *et al*[14] | 2017 | -TS  -SS  -IS  -ES | 212 | This was a continuation of the above study from 24 to 52 wks  Patient randomized into two groups:  -Placebo with 24 ml saline  -Intralesional injection of Cx601 cells | 35-40% patients withdrew before end of study  59.2% patients with Cx601 *vs* 41.6% patients with placebo (*P* = 0.013) achieved clinical remission  56.3% patients with Cx601 versus 38.6% patients with placebo (*P* = 0.010) achieved combined remission | TEAE: 76.7% in treatment group and 72.5% in control group: anal abscess/fistula.  8.7% treatment group and 8.8% control group withdrew. | Cx601 is safe and effective for treatment refractory complex perianal fistulas in patients with CD |
| Wainstein *et al*[15] | 2018 | -TS  -IS  -Pouch-vaginal | 9  (2 of 9 patients had 2 fistulas, so total fistula count was 11) | Two part study including:  -Examination under anesthesia, fistula mapping, drainage and seton placement  -Setons were removed 4-6 wks afterwards with ASC injected with biological plug formation | Complete healing in 10 of 11 fistulas  Partial healing in 1 of 11 fistulas | No AE or SAE | Fistulizing disease can be treated successfully with a multi-approach treatment including ASCs, platelet rich plasma, and endorectal advancement flaps |

**Table 4: Composite of allogeneic bone marrow derived stem cell therapy trials.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Yr of Study** | **Fistula site** | **Study population** | **Method of Administration** | **Healing Type of Fistula (unhealed, partially, fully)** | **Safety** | **Outcome** |
| Molendijk *et al*[1] | 2015 | -Perianal | 21 | Patients assigned to four groups with curettage then intralesional fistula tract injection with stem cells or placebo.   1. 1×107 2. 3×107 3. 9×107 4. placebo | Week 24 fistula healing for groups:  (1) 66.7% (*n* = 5)  (2) 85.7% (*n* = 5)  (3) 28.6% (*n* = 5)  (4) 33.3% (*n* = 6) | All patients reported pain and pus and/or discharge from fistula for 1 wk postoperatively  One patient in each group (1, 2, 3, and placebo) developed perianal abscess | Use of intralesional injections of 3×107 was successful in fistula healing. |

**Table 5 Summary of all clinical trials evaluating stem cell therapy for fistulizing inflammatory bowel disease.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Yr of Study** | **Fistula site** | **Study population** | **Stem Cell Therapy** | **Method of Administration** | **Healing Type of Fistula** | **Safety** | **Outcome** |
| Sanz-Baro *et al*[16] | 2015 | -RV  -Perianal | 5 | 2 patients with Autologous ASC injected into fistula  3 patients with Allogeneic ASC injected into fistula | All 5 patients treated with either autologous or allogeneic ASCs and achieved remission who became pregnant were given data collection forms assessing age of treatment with ASCs, gestation age, gestational complications, any medication used during pregnancy for CD, type of delivery, fetal weight, and newborn malformations | 2 of 5 patients with gestational complications of first term abortions, fetal growth restriction, and small for gestational age  1 of 4 patients who delivered with newborn malformations of syndactyly and clinodactyly | Two of the five patients experienced gestational complications: first trimester miscarriages, fetal growth restriction, and small for gestational age | No evidence that allogeneic or autologous ASC affects fertility in women |