Fertil Steril. 2005 Apr;83(4):873-7.

Changes in cytokine levels of patients with ovarian endometriosis after treatment with gonadotropin-releasing hormone analogue, ultrasound-guided drainage, and intracystic recombinant interleukin-2.

Velasco I(1), Campos A, Acién P.

Author information:

(1)Division of Gynecology, School of Medicine, Miguel Hernández University, Campus de San Juan, Apdo. 18, 03550 San Juan, Alicante, Spain. ivelasco@umh.es

OBJECTIVE: To determine the changes in cytokine levels from women with endometriomas who are treated with recombinant interleukin-2 after ultrasound-guided cyst aspiration, and to relate these changes to the clinical results observed in these patients.

DESIGN: A double-blind randomized controlled trial.

SETTING: University hospital.

PATIENT(S): Twenty-four women with endometriosis-related symptoms and endometriomas.

INTERVENTION(S): Endometriomas in women receiving GnRH analogues and undergoing transvaginal ultrasound-guided cyst aspiration were injected with dextrose that did or did not contain recombinant interleukin-2 (IL-2). Serum samples were collected before and after treatment.

MAIN OUTCOME MEASURE(S): Serum samples were analyzed by enzyme immunoassay to determine the levels of IL-1beta, IL-2, IL-6, IL-8, IL-10, IL-12, IL-13, and IL-17.

RESULT(S): The cytokine levels after treatment with GnRH analogues and recombinant IL-2 were similar to the initial levels. The patients receiving GnRH analogues without IL-2 had higher IL-1, IL-2, IL-8, and IL-13 levels. Good clinical results were observed in 90% of the patients in the first group but in only 30% of the second one.

CONCLUSION(S): Administration of recombinant IL-2 intracystically decreases cytokine production in women with endometriomas. These results have important implications for the design of future therapies based on immunomodulation, such as using higher or repeated doses of recombinant IL-2 in the cysts.

DOI: 10.1016/j.fertnstert.2004.10.035
PMID: 15820793 [Indexed for MEDLINE]

Eur J Obstet Gynecol Reprod Biol. 2008 Feb;136(2):243-8. Epub 2007 Jan 8.

The effect of intraperitoneal interleukin-2 on surgically induced endometriosis in rats.

Quereda F(1), Bermejo R, Velasco I, Campos A, Acién P.
Author information:
(1)Division of Gynecology, School of Medicine, Miguel Hernández University, Alicante, Spain. fj.quereda@umh.es

OBJECTIVE: To evaluate the effect of interleukin-2 (IL-2) on an experimental model of endometriosis.
STUDY DESIGN: Double blind and randomized experimental prospective placebo-controlled study. Experimental endometriosis was induced in 66 three-month-old female Wistar rats, by auto-transplanting fragments of endometrium to the peritoneum. After four weeks, the size of each implant was measured in millimeters by laparotomy (L2), and animals were randomly distributed for intraperitoneal administration of human-IL-2, rat-IL-2 or placebo. Four weeks later, the implants were measured (L3) and a second dose was given. After four weeks, endometriosis size was evaluated again (L4).
RESULTS: We found a reduction of experimental endometriosis at L3 that was only

significant in IL-2 treated groups: 20.1% and 30.3% with human-IL-2 and rat-IL-2, respectively ($p<0.001$ with respect to L2 size), versus a non-significant reduction of 9.0% found in placebo group, but the differences were not statistically significant between groups. The decrease after a second dose (L4) was: 49.8%, 41.8% and 11.4% with human-IL-2, rat-IL-2 and placebo, respectively ($p<0.001$ in IL-2 groups versus L2 and L3, and $p<0.05$ in both groups versus placebo at L4).

CONCLUSION: Intraperitoneal administration of IL-2 reduces experimental endometriosis, and this effect is similar using rat-IL-2 or human IL-2 (non specie-specific effect).

DOI: 10.1016/j.ejogrb.2006.11.021

PMID: 17208346 [Indexed for MEDLINE]

J Reprod Immunol. 2007 Jun;74(1-2):124-32. Epub 2007 Jan 8.

Intraperitoneal recombinant interleukin-2 activates leukocytes in rat endometriosis.

Velasco I(1), Quereda F, Bermejo R, Campos A, Acién P.

Author information:

(1)Division of Gynecology, School of Medicine, Miguel Hernández University, Alicante, Spain. ivelasco@umh.es

The aim of this double-blinded study was to determine changes in leukocyte populations in blood, peritoneal lavage fluid, eutopic and ectopic endometrium after treatment with recombinant rat interleukin-2 (IL-2) using an in vivo experimental model of rat endometriosis. The in vivo model involved transplanting four square fragments of autologous endometrium onto the inner surface of the

abdominal wall in 20 Wistar rats. The control group was constituted by 20 sham-operated rats. Both groups were randomly treated (1-month interval treatment) with 2 intraperitoneal doses of glucose solution (5%) that did or did not contain recombinant IL-2, and animals were sacrificed 4 weeks after the last dose of treatment. Blood and peritoneal lavage were obtained during the initial and final laparotomy, whereas eutopic and ectopic endometrium were collected at the end of the experiment. Endometriotic implants were measured in each laparotomy to determine any change in size. Leukocyte populations were analyzed by flow cytometry and immunofluorescence microscopy. Cytometric results were similar in blood and peritoneal lavage. CD25+ and natural killer (NK) cell levels in peripheral blood were lower in rats with endometriosis treated with IL-2, whereas NK cells increased in lavage compared to placebo group. The percentage of macrophages and dendritic cells in blood were higher in all rats treated with IL-2, as well as peritoneal dendritic cells. Implant size of these rats decreased significantly, showing a greater number of activated lymphocytes, macrophages, NK and dendritic cells inside them. In conclusion, recombinant IL-2 induced recruitment of activated leukocytes into endometriotic-like foci, and this was related to a reduction of the implant size, suggesting potential effectiveness of IL-2 as an immunomodulatory agent in this pathology.

DOI: 10.1016/j.jri.2006.12.001

PMID: 17210185 [Indexed for MEDLINE]

Gynecol Obstet Invest. 2010;69(3):203-11. doi: 10.1159/000270901. Epub 2009 Dec 24.

Treatment of endometriosis with transvaginal ultrasound-guided drainage and recombinant interleukin-2 left in the cysts: a third clinical trial.

Acién P(1), Velasco I, Acién M, Quereda F.

Author information:

(1)Service of Obstetrics and Gynecology, San Juan University Hospital, Department/Division of Gynecology, School of Medicine, Miguel Hernandez University, Campus of San Juan, Alicante, Spain. acien@umh.es

BACKGROUND: To analyze the therapeutic results of recombinant interleukin-2 (rIL-2) left in the cysts after transvaginal ultrasound (US)-guided drainage of endometriomas as an alternative to surgery.

METHODS: Prospective and randomized clinical trial. A total of 25 consecutive patients were included. Two transvaginal US-guided punctures were performed, and 3 million IU of rIL-2 were left in the aspirated cysts once (group I) or both (group II) times according to randomization.

MAIN OUTCOME MEASURES: Clinical results, prevented surgeries, and recurrences.

RESULTS: Results were moderate or good in only 16% of subjects at 3 months and in 33% of subjects at 6 months after treatment in group I; these numbers were 66 and 33%, respectively, in group II. Differences were not statistically significant. However, the evolution of symptoms, endometriomas, and CA-125 revealed the low efficacy of rIL-2 left intracyst as well as a poor control of the clinical manifestations. After 1 year, 20% (group I) and 73% (group II) of patients had to be operated; after 2 years, these numbers were 55 and 82%, respectively.

CONCLUSIONS: Treatment of endometriomas with transvaginal US-guided drainage and rIL-2 left in the cysts, without using endometrial suppressive therapy with GnRH analogues as done in previous studies, has low efficacy. Recurrences are even more frequent after the use of two rIL-2 doses.

DOI: 10.1159/000270901

PMID: 20051692 [Indexed for MEDLINE]

Gynecol Obstet Invest. 2005;60(4):224-31. Epub 2005 Oct 21.

Treatment of endometriosis with transvaginal ultrasound-guided drainage under GnRH analogues and recombinant interleukin-2 left in the cysts.

Acién P(1), Pérez-Albert G, Quereda FJ, Sánchez-Ferrer M, García-Almela A, Velasco I.

Author information:

(1)Service of Obstetrics and Gynecology, San Juan University Hospital and Department of Gynecology, School of Medicine, Miguel Hernandez University, Campus of San Juan, Alicante, Spain. acien@umh.es

BACKGROUND: To analyze the therapeutic results of one dose of 3 million IU of recombinant interleukin-2 (rIL-2) left intracyst (group I) versus two doses with a 1-month interval (group II) after transvaginal ultrasound (US)-guided drainage of endometriomas under the effect of GnRH analogues.

METHODS: Prospective and randomized clinical trial (helped by a random number table) at a University Hospital. Twenty-four consecutive patients with endometriomas initially sent to us for laparotomy and conservative surgery for endometriosis were included.

INTERVENTIONS: Treatment with GnRH analogues every 28 days, 3 doses. Under their effect, one or two transvaginal US-guided punctures were performed in order to aspirate the endometriomas, and 3 million IU of rIL-2 were left in the aspirated cysts each time.

MAIN OUTCOME MEASURES:

CLINICAL RESULTS: two menstruations after GnRH analogues. Other secondary outcome measures were: the time until recurrence of cysts, symptoms and CA-125 >35 U/ml, and the need for further medical or surgical treatment.
RESULTS: They were moderate or good in >50% of cases with one drainage and one dose of 3 million IU of rIL-2 intracyst, but were better with a second drainage and two doses of rIL-2 (25 vs. 58.3% 'good results'). There were fewer recurrences and the interval before recurrence was longer after two doses but differences were not significant. Six patients from group I (50%) and 3 from group II (25%) needed laparotomy and conservative surgery at 17.5 +/- 8.7 months (total time of follow-up = 33 +/- 8.8 months).
CONCLUSIONS: Treatment of endometriomas with transvaginal US-guided drainage and rIL-2 left in the cysts under endometrial suppressive therapy with GnRH analogues has beneficial effects, improving clinical manifestations and avoiding some surgical therapies. The use of a higher dose of rIL-2 does not produce better results, whereas drainage + rIL-2 twice does.

DOI: 10.1159/000089100

PMID: 16244488 [Indexed for MEDLINE]

Gynecol Obstet Invest. 2003;55(2):96-104.

GnRH analogues, transvaginal ultrasound-guided drainage and intracystic injection of recombinant interleukin-2 in the treatment of endometriosis.

Acién P(1), Quereda FJ, Gómez-Torres MJ, Bermejo R, Gutierrez M.

Author information:

(1)Services of Obstetrics and Gynaecology, San Juan University Hospital, School of Medicine, Miguel Hernandez University, Campus of San Juan, Alicante, Spain.

acien@umh.es

We performed a double-blind, randomised controlled trial to evaluate the results of ultrasound-guided aspiration of endometriomas under the effect of GnRH analogues and a possible additional beneficial effect by leaving 600000 IU of recombinant interleukin-2 (rIL-2) in the cysts. Twenty-four women with endometriosis-related symptoms, increased values of CA-125 and transvaginal ultrasonography showing endometriomas >3 cm who were initially sent to us for laparotomy and conservative surgery for endometriosis were included. Main outcome measures were severity of symptoms, size and percentage of echographical reduction of endometriomas and CA-125 levels after 2 menses post-GnRH analogues. Secondary outcome measures were the time until recurrence of abnormal parameters and the need for surgery after treatment. We found moderate clinical results after treatment with drainage plus GnRH analogues and significantly improved results in women having received rIL-2 intracystically. There were no side effects. Two out of 3 previously infertile patients became pregnant after therapy. Though the rates of recurrence of endometriomas >or=3 cm were similar in both groups, the period until recurrence was significantly greater when rIL-2 was used, and the rates of recurrence of symptoms and increased CA-125 values were also significantly lower in patients who received rIL-2. Surgery was finally performed on 10 patients (4 with and 6 without previous rIL-2 treatment) during follow-up (30 +/- 12.7 months). These findings led to the conclusion that transvaginal ultrasound-guided puncture and aspiration of endometriomas under endometrial suppressive therapy with GnRH analogues have some value for endometriosis treatment, improving the clinical manifestations and avoiding some surgical therapies, and that rIL-2 left in the cyst increases these beneficial effects significantly.

DOI: 70181

PMID: 12771456 [Indexed for MEDLINE]