Clinical use of nafarelin in the treatment of leiomyomas: a review of the literature

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Authors’ objectives
To review the efficacy and safety of nafarelin in the treatment of leiomyomas.

Searching
MEDLINE and Refline were searched from 1986 to 1997 using the subject headings: 'leiomyoma', 'fibroids', 'nafarelin' and 'gonadotropin-releasing hormone agonists'. The bibliographies of retrieved articles were manually searched, as were relevant journals and abstracts from conferences and other meetings held during the 12-year period of interest.

Study selection
Study designs of evaluations included in the review
Only published trials reported in peer-reviewed journals, non-reviewed journals or technical reports, or as conference presentations were eligible. Studies included were: a randomised placebo-controlled trial, a randomised phase II dose ranging study, a phase III randomised double-blind double-dummy comparison trial, and open non-comparative trials. The trial ranged in duration from 24 weeks to 9 months, or until abdominal hysterectomy was performed.

Specific interventions included in the review
Intranasal nafarelin at a dose of 50 to 400 microg twice daily for 3 to 6 months. The comparators found in the included studies were placebo for 3 months, and buserelin at a dose of 300 microg twice daily for 16 weeks.

Participants included in the review
Women with symptomatic leiomyomas were included.

Outcomes assessed in the review
The primary outcomes assessed were: vaginal bleeding patterns, i.e. changes in menorrhagia or menometrorrhagia; leiomyoma and uterine size, as measured by ultrasound or magnetic resonance imaging; surgical conditions; and safety measures such as adverse effects, bone loss and changes in the laboratory. The secondary outcomes were changes in haemoglobin and anaemia, changes in serum estradiol (E2), and any information regarding the surgical experience and intra-operative conditions.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection. However, they do state that the papers were carefully reviewed using a systematic method of content analysis.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted for the following categories: study identification, study design, treatment (daily dose and duration), the number of patients enrolled, efficacy variables, safety variables, and the length of post-treatment follow-up.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative summary, grouped according to outcome measure.
How were differences between studies investigated?
The authors do not state a method for assessing any heterogeneity.

Results of the review
Six studies with 602 participants were included in the review: 3 open, non-comparative trials (n=33); 1 randomised, double-blind placebo-controlled trial (n=101); 1 phase II, randomised, dose-ranging study (n=257); and 1 phase III, randomised, double-blind, double-dummy comparison (n=211).

Menorrhagia and menometrorrhagia (4 trials): amenorrhoea developed in a large proportion (51 to 100%) of women, and in summary, nafarelin reduced uterine bleeding within 4 months of treatment initiation. Amenorrhoea and reduced uterine bleeding resulting from nafarelin treatment were associated with a rise in mean haemoglobin concentrations.

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Haemoglobin concentrations, anaemia, and other haematologic tests (4 trials): in all studies, nafarelin treatment resulted in a rise in mean haemoglobin concentrations; the change from baseline was reported to be statistically significant in three of the studies. Nafarelin improved haematologic parameters in women with and without anaemia.

Leiomyoma volume (5 trials with 450 participants): all trials documented that mean leiomyoma size decreased after nafarelin treatment. The mean changes in leiomyoma volume after 3 to 6 months of treatment ranged from -31 to -59%. Significant reductions in leiomyoma size were noted within the first month of treatment in several studies. In the one comparator trial, nafarelin and buserelin decreased leiomyoma size similarly. The monthly rates of change levelled off in most nafarelin groups after the first 3 months of treatment, although tumour regression was dose dependent in one study. Regrowth was noted in some trials.

Uterine volume (5 trials with 450 participants): all trials documented that the mean uterine size decreased after nafarelin treatment. The uterine weight (mean plus or minus the standard deviation) following hysterectomy was also significantly lower in the nafarelin group than in the placebo: 255.5 (+/- 12.6) g and 346.2 (+/- 35.7) g, respectively (p=0.29). Significant reductions in uterine size were noted in the first month in several studies; further reductions occurred with each month of treatment; and the rate of change appeared to decrease after 3 months of treatment. Nafarelin discontinuation was generally associated with a return to pre-treatment size within 3 to 4 months after treatment discontinuation.

Hysterectomy and myomectomy (1 trial and 4 cases): there were no statistically-significant differences between the nafarelin and placebo groups with regard to surgical duration, blood loss during surgery, or surgeon-rated surgical conditions (vascularity, visibility and mobilisation). In the 4 cases, myomas were easily separated from the surrounding myometrium with minimal blood loss.

Measured bone mineral density (3 trials with 81 participants): this decreased significantly during treatment, although by 6 to 9 months post-treatment, it had increased to values not significantly different from baseline.

Nafarelin suppressed serum E2 hormone concentrations and exhibited dose dependency in this effect (p=0.0006). Nafarelin improved patients' symptoms. There were no significant differences between the nafarelin and placebo groups regarding changes to the endometrium and myometrium.

Nafarelin was well tolerated. Hot flushes were the most commonly reported adverse event (range: 38.5 to 100%). The adverse effects of nafarelin were generally reversible after treatment withdrawal.

Authors' conclusions
The authors state that nafarelin treatment of women with symptomatic leiomyomas effectively decreases uterine bleeding, improves haematologic parameters, manages symptoms of menometrorrhagia, dysmenorrhoea and pelvic discomfort, reduces uterine and myoma size, and is well tolerated. Reduction in bone mineral density occurs, but levels return to approximately baseline levels within 6 months of treatment discontinuation. Patients can be expected to benefit from pre-operative use of nafarelin.
CRD commentary
The authors have clearly stated their research question, but the inclusion and exclusion criteria were limited. The literature search was limited by searching only one electronic source and by restricting it to published trials only. In addition, it was not stated whether there were any language restrictions. Although additional sources were checked, it is possible that some studies may have been missed. The authors do not report who, or how many of the authors, selected the studies or extracted the data. There was no validity assessment of the included studies.

Data were extracted and presented in tables, whilst individual studies were reviewed in the text. The review was a narrative discussion with no statistical pooling. There was no discussion of the differences between the included studies. Bias is possible considering the review was sponsored by the manufacturers of nafarelin.

The authors’ conclusions appear to follow from the results, but should be viewed with caution because of the methodological limitations in the review process.

Implications of the review for practice and research
Practice: The authors state that decisions on treatment may be made on the basis of individual patient response and other characteristics, such as age, desire to avoid surgery and osteoporosis risk.

Research: The authors did not state any implications for further research.

Funding
G. D. Searle and Co., Skokie, USA.

Bibliographic details

PubMedID
10900582

Indexing Status
Subject indexing assigned by NLM

MeSH
Abdominal Pain /prevention & control; Clinical Trials as Topic; Female; Hormones /therapeutic use; Humans; Leiomyoma /drug therapy; Menorrhagia /prevention & control; Nafarelin /therapeutic use; Pregnancy; Uterine Neoplasms /drug therapy

AccessionNumber
1200001298

Date bibliographic record published
31/03/2002

Date abstract record published
31/03/2002

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.