Goserelin treatment in glandular hyperplasia

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Summary: Glandular Hyperplasia is commonly associated with meno and/or metrorrhagia. We treated 84 patients suffering from meno and/or metrorrhagia associated with simple glandular hyperplasia with a gonadotropin releasing hormone agonist, goserelin, (Zoladex, ICI Pharmaceuticals, Macclesfield. Cheshire, England), available in a depot formulation.

Subcutaneous administration of goserelin 3.6 mg was repeated every 28 days for 6 months. Within the first 4 weeks from the start of therapy 45% of the patients became amenorrhoeic, within 12 weeks 100%. Only 3 patients reported continued spotting.

Hysteroscopic evaluation and biopsy have shown in the 84 evaluable patients, a positive result in 76 (90.4%), demonstrating the validity of the use of this analogue in this indication.

In the future it would be of value to increase the period of treatment in selected cases as well as increasing the length of the follow-up period.

Key words: GnRH analogue; Therapy; Uterine hyperplasia; Metrorrhagia.

INTRODUCTION

Many varied morphological states may be considered classifiable as Endometrial Hyperplasias, ranging from cases very close to normal mucosal endometrium to frank dysplastic states. A more correct approach is to distinguish between low and high risk hyperplasia, (adenomatous hyperplasia with or without cytonuclear atipia), which in the natural evolution of adenocarcinoma of the endometrium are considered its precursors.

The administration of a GnRH analogue, (GnRHa) in a continuous manner, (chronic administration), results in a desensibilisation accompanied by a loss in responsativeness to GnRH, (down regulation), and hence hypertrophy of the target organs ([7, 8, 9, 10]). This discovery has led to the clinical use of GnRH analogues in varying fields such as: prostate cancer, breast cancer, endometriosis, hirsutism, precocious puberty and uterine fibroids ([1, 2, 3, 4, 5, 6, 16, 18, 20]).

Their use in our opinion may be extended to glandular hyperplasia of the endometrium. This is an extremely widespread pathology in perimenopausal women in whom the neoplastic potential varies, according to the form, from 0.4% to 80%.

The object of this study was to evaluate the efficacy of treatment with the GnRHa, goserelin (Zoladex, ICI Pharmaceuticals, Macclesfield, Cheshire, England) ([14, 15, 17, 19, 21, 22]) in meno and/or metrorrhagia caused by simple cystic glandular hyperplasia of the endometrium, both in terms of reducing bleeding and of objective impro-

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vement in the hysteroscopic endometrial profile.

Eighty-four patients were recruited after undergoing a diagnostic hysteroscopy for perimenopausal menometrorrhagia or menopausal metrorrhagia at the "Service for Precocious Diagnosis and Therapy af Tumours of the Feminine Genital Apparatus" based in the II Department of Gynaecological Oncology of the University of Catania.

The identification, monitoring and treatment of these precursors can result in the primary prevention of adenocarcinoma of the endometrium.

MATERIALS AND METHODS

Starting from 1st March 1989, 84 patients were recruited into our study. All, at the point of entry into the study, were suffering from metrorrhagia or menometrorrhagia. Hysteroscopy and subsequent histological investigation resulted in a diagnosis of Glandular Endometrial Hyperplasia. The women were aged from 38 to 55 and had suffered from metrorrhagia or menometrorrhagia for a period of between 1 and 12 months.

The patients had not received medical therapy, including progestins, danazol and/or other LHRH analogues during the two years preceeding their entry into the study. The number of pregnancies ranged from 1 to 9, mean 3.4, (only one patient had never been pregnant).

Of the 84 patients, 67 had simple hyperplasia, 10 glandular polyploidal hyperplasia and 7 microcystic hyperplasia (Table 1).

Goserelin is available in the form of a biodegradable depot in which the decapeptide is dispersed throughout a lactide-glycolide polymer matrix. All patients received a subcutaneous injection of goserelin 3.6 mg into the abdominal wall every 28 days for 6 cycles. To be eligible for the study the patient had to be over 38 years old and be suffering from metrorrhagia and/or menometrorrhagia substained by at least one of the following:

- simple glandular endometrial hyperplasia;
- polyploidal glandular hyperplasia;
- microcystic glandular hyperplasia.

Exclusion criteria included the presence of adenomatous hyperplasia with atypical cytonuclearity or the presence of adenocarcinoma.

The patients were subjected to the following clinical examinations:

Before treatment – hysteroscopy with biopsy. The biopsy was undertaken by removing a very small amount of tissue; however, for the biopsy a currettage was performed.

At the end of the third cycle of treatment (20 days after the third injection) and at the end of treatment. (30 days after the last injection) hysteroscopy was performed.

Six months after treatment suspension, (end of follow-up period) - a further hysteroscopy and eventual biopsy were performed.

Throughout the treatment period the following pharmacological side effects were recorded: intensification of the metrorrhagia after the first injection, nausea, headaches, hot flushes, bone pain, local reactions at the site of injection, variation in weight, reduction in libido and allergic reactions.

Table 1.

Hyperplasia	No cases
Simple Glandular	67
Polyploidal Glandular	10
Microcystic Glandular	7
Total	84

RESULTS

All the 84 patients who entered the study completed the 6 cycles of therapy and undertook the two control hysteroscopies, at the and of treatment and at the end of the follow-up period.

In the case of severe metrorrhagia coagulating therapy was used in order to be able to perform the hysteroscopy correctly. In 6 cases there was a worsening of the metrorrhagia subsequent to the first injection, which was resolved by the second.

Amenorrhea was acheived in 38, (45%) of the patients after the first depot, 81, (96%) after the second and 84, (100%) after the third. In three out of the seven cases of microcystic glandular hyperplasia, persistent spotting occurred throughout the treatment period.

Sixty-one patients reported side effects comprising: sympathetic effects, (hot flushes, headaches and nausea), 55 pa-

Table 2. — *Hysteroscopic modifications according to pre-treatment classification.*

Pre treatment	After 3 cycles of LHRHaa	After 6 cycles of LHRHaa	After 12 months follow-up
Simple Hyperplasia (67 cases)	23 hypotrophy 44 atrophy	9 hypotrophy 58 atrophy	2 simple hyperplasia 6 hypotrophy 11 atrophy 7 active asynchronous 41 active synchronous
Polyploidal Hyperplasia (10 cases)	2 partial hypotrophy 5 hypotrophy 3 atrophy	5 hypotrophy 5 atrophy	3 polyploidal hyperplasia 2 hypotrophy 4 active asynchronous 1 atrophy
Microcystic Hyperplasia (7 cases)	1 focal hyperplasia 6 partial hypotrophy	2 focal hyperplasia 4 hypotrophy 1 atrophy	3 microcystic hyperpl. 3 hypotrophy 1 atrophy

tients; bone pain (vertebral or pelvic), between the third and sixth depot, 27 patients; local reactions at the site of injection, 2 patients; increase in weight of 8 kg, 1 patient.

Efficacy as determined via hysteroscopy and biopsy at the various stages of the study are reported in Table 2.

By the end of the follow-up period the objective results could be summarised as follows: in 24 patients (28.5%) amenorrhoea persisted; 13 of these were considered to have reached the natural menopause (the episode of metrorrhagia began after a previous period of amenorrhoea lasting between 1 and 3 years, the patients possessed both clinically and hormonally a menopausal profile). The corresponding hysteroscopic results showed 13 cases of atrophic endometrium and 11 cases of hypotrophic endometrium.

In 52 cases (61.9%) the return of menses was accompanied by a normal flow. The corresponding hysteroscopic evaluation showed synchronous active endometrium in 41 cases.

In 8 patients (9.5%) menometrorrhagia and intermenstrual metrorrhagia occurred, possessing the same characteristics as prior to treatment. Equally the hysteroscopic evaluation revealed the same endometrial profile as prior to therapy, (2 cases simple hyperplasia, 3 polyploid hyperplasia, 3 microcystic hyperplasia).

No significant modifications were seen in the routine laboratory analysis performed.

CONCLUSIONS

In all the patients recruited into the study a complete remission of the symptoms occurred, in the majority of cases within the second administration of the depot, which lasted throughout the treatment period.

It is thus possible to use goserelin depot in order to arrest metrorrhagia in a stable manner. A therapeutic option particularly useful in patients who should undergo surgery but in whom surgery is contraindicated for various reasons such as diabetes, cardiovascular problems and anaemia.

A correlation was shown to exist between the reduction of symptomatic blee-

ding and an improvement in the hysteroscopic and histological profile, both of which persisted throughout the treatment period.

If recognised pharmacological side effects are excluded, especially the hot flushes which occured in nearly all patients, it can be said that no side effects of a serious nature occurred. The recognised pharmacological side-effects were not of sufficient gravity to provoke the withdrawal of any patient or the administration of other drugs in order to render then more tolerable.

The results obtained upon examination at the end of the follow up period, (Fig. 1), showed that 76 of the 84 patients (90.47%) benefited from the treatment. In 41 of the 52 patients the return of the menstrual cycle brough regular menstrual flow combined with a normal endometrium upon hysteroscopy; whereas 13 of the 24 considered to be menopausal remained in amenorrhoea.

In 8 cases (9.5%) in which the 12 month follow-up showed a return to meno and/or metrorrhagia 3 were shown to have microcystic hyperplasia, 3 polyploidal hyperplasia and 2 simple hyperplasia. However, given, the clinical response to the therapy, in terms of a reduction in bleeding, it would be interesting to prolong the duration of goserelin therapy in these selected cases. In conclusion therefore it is our opinion that the administration of this analogue in the form of a depot is justified by the response rate ot 76/84 (90.47%), combined with the scarsity of side effects. A longer period of follow-up and the use of the drug for more than 6 months would, in selected cases, allow a more profound investigation of the real and definite efficacy of the use of goreselin in the treatment of meno and/or metrorrhagia associated with glandular endometrial hyperplasia.

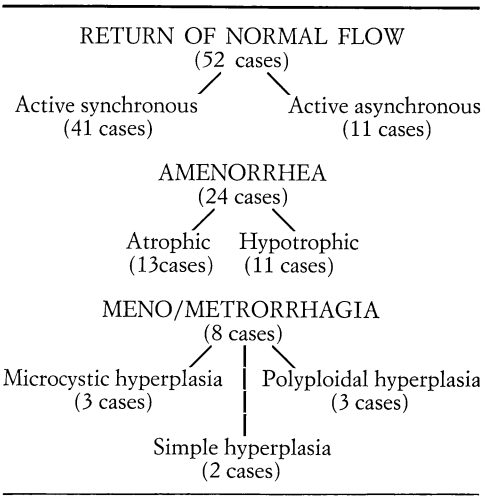

Fig. 1. — Final hysteroscopic evaluation according to bleeding status post-treatment.

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