Introduction

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This publication summarizes the presentations and discussions that took place at a round-table meeting that was held to review the current and future role of gonadotropin-releasing hormone (GnRH) analogues in the management of endometriosis. The meeting took place on 12 March 2008 during the 10th World Congress on Endometriosis in Melbourne, Australia. The program for the meeting comprised state-of-the-art scientific and clinical presentations given by an international panel of experts.

In the first session, presentations by Dr. Osuga (Japan) and Dr. Tesone (Argentina) gave a pathophysiological perspective on novel therapeutic targets in endometriosis and the role and underlying mechanism of action of GnRH analogues in this disease based on data from the latest preclinical studies. In the second session, Dr. Laufer (USA) gave an expert perspective on optimizing the treatment of endometriosis in an important patient group: adolescents.

It has previously been considered that the therapeutic effect of GnRH analogues on endometriosis can be explained by the suppression of estrogen levels due to pituitary downregulation; however, Dr. Osuga described recent exciting research by his group on the pathogenesis of endometriosis that suggests that the effect may be exerted by multiple mechanisms. One example is the inhibition of ovulation caused by GnRH analogues, which results in a reduction in the exposure of endometriotic lesions to midkine – a growth factor present in ovarian follicular fluid that has angiogenic, mitogenic, and che-

motactic activities, and is thought to be involved in the proliferation of endometrial cells and development of endometriosis. He also described studies suggesting that the inhibition of bleeding caused by GnRH analogue therapy can reduce the exposure of endometriotic lesions to thrombin. Thrombin, which is produced in the process of coagulation, and its specific receptor, protease-activated receptor 1 (PAR1), are important factors in inflammation and cell proliferation and are thought to be involved in the pathophysiology of endometriosis. Abnormal uterine contractions have been observed in women with endometriosis, and it has been postulated that the resulting mechanical stretch might stimulate the production of pro-inflammatory mediators, such as interleukin-8 (IL-8), as has been observed in studies with endometrial stromal cell cultures. Thus, Dr. Osuga concluded, the inhibition of uterine contractions by GnRH analogue therapy, in particular during menstruation, would also block the mechanical stress on the endometrium, suppress the production of IL-8, and ultimately inhibit the development of endometriosis. He also noted the importance of the T-cell immune response in endometriosis. It has been argued that endometriosis is an inflammatory disease and its development is associated with an abnormal T-cell function. Dr. Osuga proposed a 'T-cell immune network hypothesis' to explain the etiology of the disease. Various types of T-helper (Th) cells – Th1, Th2, Th17 and regulatory T cells – each producing their own specific cytokine, interact with each other in a network. If the usual balance

is disturbed, an excess of pro-inflammatory cytokines, such as IL-4 or IL-17, can lead to the development of endometriosis.

Dr. Tesone gave an overview of some of the other pathophysiological mechanisms involved in the development of endometriosis, namely apoptosis, cell growth and angiogenesis. She postulated that GnRH analogues acted directly on endometrial cells and inhibited their growth and proliferation by regulation of apoptotic and angiogenic mechanisms. Dr. Tesone's research group has performed studies which show that eutopic endometrial cells from patients with endometriosis show an increased proliferation rate and are less susceptible to cell death by apoptosis than those from subjects without the disease. Notably, the GnRH analogue, leuporelin, was found to inhibit cell proliferation and increases the apoptotic rate in eutopic endometrial cell cultures. She suggested that this increase in apoptosis appeared to be mediated by an increase in the expression of the pro-apoptotic proteins Bax and FasL and a decrease in the expression of the anti-apoptotic protein Bcl-2. Angiogenesis – the development of new blood vessels from pre-existing vessels – is an important stage in the development of endometrial tissue, and is regulated by vascular endothelial growth factors (VEGFs) and angiopoietins. VEGF levels are known to be elevated in peritoneal fluid from patients with endometriosis and in the endometriotic tissue itself. In addition, it has been demonstrated that the expression of VEGF is potentiated by a variety of cytokines, including IL-1 β . Dr. Tesone described recent studies showing that leuporelin reduces the production of VEGF-A and IL-1 β in eutopic endometrial cell cultures, suggesting a mechanism by which it could inhibit the development of endometriosis. She concluded that GnRH analogues are effective in reducing the growth of endometrial cells not only by the classical endocrine effect but via a direct effect on the cells themselves, and that this knowledge may contribute to the development of improved therapies for this debilitating disease.

Endometriosis is known to occur in adolescents as young as eight years of age and this patient group presents particular challenges in terms of differential diagnosis, variable presentation and symptoms, and choice of treatment. In addition, long-term outcomes of therapy have not been studied in this age group. Dr. Laufer reviewed the latest advances in the diagnosis and treatment of adolescent endometriosis and described how this could be optimized, and the pitfalls to be avoided. He confirmed the importance of early diagnosis in these patients in order to decrease pain and prevent disease progression – however, whether early diagnosis and treatment preserved future

fertility was currently an unanswered question. He considered that surgery in this patient group was cytoreductive rather than curative and that postoperative medical therapy should be initiated regardless of disease stage.

Treatment with a GnRH agonist is one of the therapeutic options commonly utilized for endometriosis patients, and while these agents are recognized to be extremely effective in relieving symptoms, they may not be considered for long-term use due to possible adverse effects on bone mineralization. This consideration is of particular importance in adolescents who are at a critical age for accrual of bone mineral density (BMD), but Dr. Laufer advised that any potential problems of bone loss with GnRH therapy may be able to be avoided with the use of 'add back' therapy. He reported the results from a recent clinical study by his group showing that most adolescents with endometriosis receiving a GnRH agonist plus add-back therapy with norethindrone acetate had normal BMD at the hip. Dr. Laufer found that add-back therapy appeared to be a promising adjunct to GnRH agonist therapy for the prevention of bone loss in endometriosis patients since the administration of low doses of a steroid hormone (such as estradiol, norethindrone, or medroxyprogesterone) preserves bone density without negatively impacting the primary therapeutic effect of the GnRH agonist. It could also allow longer-term therapy than with a GnRH agonist alone. He recommended, however, that BMD should continue to be carefully monitored after the initial 6–8 month period of therapy and then approximately every two years in adolescent patients (over age 16) receiving long-term GnRH agonist therapy. He also stressed the importance of calcium and vitamin D supplementation.

We would like to extend our gratitude to the international faculty who took part in this meeting for their valuable contributions and informative feedback during the discussion sessions, which allowed us to gain valuable expert insight into these issues. We would also like to acknowledge the continuing generous sponsorship of Takeda Pharmaceutical Company Ltd., which made the meeting possible.

Disclosure Statement

Professor Terakawa has no conflict of interest to disclose.