Combined treatment of gestrinone with histone deacetylase inhibitors for the treatment of deep endometriosis-associated pain

Abstract ID : 2432
Submitted by : Hugo Maia Jr. the 2017-01-18 14:04:34
Category : SEUD CONGRESS
Typology : Communication orale / Oral communication
Status : Validated
Authorisation to disclose : Yes/Oui

Objective: The present study was designed to investigate the effects of valproic acid or resveratrol with vitamin D3 in Pentravan®, administered vaginally, on deep endometriosis-associated pain in patients undergoing treatment with gestrinone. Theoretically, this combination would result in much faster pain relief, since both medications are enzymatic inhibitors of several histone deacetylase (HDAC) isoforms whose activity is enhanced in endometriosis patients.
Material and Methods: This was an open study involving 33 patients with deep endometriosis and pelvic pain unresponsive to previous progestin-based treatment. Pain was assessed at the initial visit and after the first and third months of treatment according to a visual analog scale (VAS) graded from 0 to 10. Hysteroscopy with endometrial biopsy (n=21) was performed before and after the first month of treatment to determine aromatase expression by immunohistochemistry. Patients were divided into three groups. Patients in Group I (n=16) were treated for 6 months with vaginal gestrinone (5 mg/ml) twice a week together with pycnogenol (100 mg) and silymarin (400mg) administered orally every day. In Group II (n=8), the patients received the same treatment together with vaginal resveratrol (100mg/ml) and vitamin D3 (5000U/ml) administered daily. Patients in Group III (n=9) were treated with gestrinone together vaginal valproic acid (250 mg) administered daily. All vaginal medications were given in Pentravan®
Results: There was a significant decrease in the mean pain score of patients in Group I from 9 at baseline to 3 after the first month of treatment. In Groups II and III, on the other hand, the pain score decreased from a mean of 9 to a mean of 1, a significantly greater decrease than that achieved in Group I (p=0.01). Although the reduction in pain was significant in all the groups, it was much greater in the groups treated simultaneously with HDAC inhibitors after the first month of treatment. By the third month of treatment, all patients in all three groups were amenorrheic and pain free. Aromatase expression was still positive in 80% of endometria in Group I after the first month of treatment (8/10). However, in Group II, only 12% (1/8) of the endometria remained positive for aromatase expression, a significantly lower percentage than in Group I (p=0.006). In Group III, aromatase expression was detected in the first month in 2/3 patients (66%). This percentage was significantly higher than that of Group II (12%) (p=0.04) but not different from that of Group I (80%).
Conclusion: The use of HDAC inhibitors in Pentravan® potentiated the pain-relieving effects of gestrinone in patients with deep endometriosis in the first month of treatment; however, this difference disappeared in the subsequent months. This suggests that if much faster pain relief were desired in cases of deep endometriosis, then a combination of vaginal gestrinone with an HDAC inhibitor would be preferable to the use of gestrinone alone. The combined use of gestrinone with epigenetic drugs is a novel and highly effective treatment for deep endometriosis-related pain.

Keywords : deep endometriosis; pain; gestrinone; Pentravan®; histone deacetylase (HDAC) inhibitors
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