An opinion on H1-antihistamines as a potential avenue for endometriosis management

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Endometriosis is a chronic inflammatory gynecologic condition among women of reproductive age causing a plethora of symptoms that significantly affect their quality of life and mental health. Recent literature reports mounting evidence for several inflammation-mediated pathways for endometriosis pathogenesis, where elevated levels of proinflammatory factors, such as intercellular adhesion molecule 1, tumor necrosis factor-alpha, and nuclear factor kappa B have been established. Simultaneously, the prevalent clinical use of H1-antihistamines for other pathologies along with active research into its action pathways has led to our current understanding that H1-antihistamines counteract several inflammation mediators, including intercellular adhesion molecule 1, tumor necrosis factor-alpha, and nuclear factor kappa B. Although a wide range of existing drug-based endometriosis managements act via the estrogen-dependent pathways, along with some newer ones attempting to use antagonists of targeted inflammation-modulating factors, investigations into the direct use of H1-antihistamines in the context of endometriosis are currently lacking. In this brief perspective opinion essay, correlative evidence has been placed forward that points toward a potential avenue of H1-antihistamines for endometriosis management, and some ideas have been highlighted for future research considerations.

Key words: Endometriosis, H1-Antihistamines, Inflammatory processes

Introduction

Endometriosis (ES) is a gynecologic disease where ectopic endometrial cells adhere to the peritoneum and other regions of the pelvis and are thought to undergo estrogen-induced proliferation in reaction to the menstrual hormonal cycle, thereby causing a range of quality-of-life–affecting symptoms among 6% to 10% of the women of reproductive age.[1] Classically, the onset of ES through ectopic endometrial cells has been attributed to the retrograde menstrual flow[2]; however, several other pathogenesis pathways involving nonuterine cells have also been proposed and studied,[3] including the coelomic metaplasia theory of the hormonal stimulus and inflammation-driven irritation.[4]

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Despite advances in different diagnostic imaging modalities, the detection of ES is often challenging, owing to the varying range of their sensitivity and specificity and the nonspecific nature of the symptoms further complicating early detection of ES.[5] Owing to these complex confusing effects, the clinical diagnosis of ES is often delayed by 4 to 11 years after the onset of symptoms.[6] Diagnostic laparoscopy is considered the "gold standard" for diagnosing ES; however, the aforementioned delays in getting to this stage are often at the cost of disease progression.[7]

Overview on existing therapeutic managements for endometriosis and H1-antihistamines

In this section, we briefly discuss the common symptomatic manifestations of ES and its management using different classes of drugs. In addition, we provide an overview of the use and side effects of a widely known class of drugs called H1-antihistamines (H1-As).

Symptoms and management of endometriosis

Chronic pelvic pain, menorrhagia, dysmenorrhea, intermenstrual pain, abdominal pain, gastrointestinal disturbances, and psychological burden (eg, depression and phobic anxiety) are some of the commonly reported symptoms of ES.[8,9] All such symptoms have been shown to significantly deteriorate the health-related quality of life for women.[10,11]

Several medications currently being used for the management of ES predominantly target its different hormonal-mediated pathways and focus on inhibiting the growth and proliferation of ectopic endometrial implants.[1] Oral contraceptives, such as combination estrogen-progesterone or low-dose progesterone-only regimes, have been a popular choice to suppress the ovaries and endometrial cell growth. Alternatively, high-dose, periodically injectable progesterone (such as medroxyprogesterone acetate) or sustained-release progesterone implants have been used to suppress endometrial cell proliferation and new vascularization to the implants. In addition, gonadotropin-releasing hormone agonists[12] and antagonists[13] are being used for the regression of endometrial implants via suppression of the hypothalamic-pituitary-ovarian axis and induction of hypoestrogenism. Similarly, aromatase inhibitors have been considered as a way to suppress estrogen synthesis and thereby growth of ES implants.[14] Furthermore, agents that inhibit the inflammatory cytokine pathways such as tumor necrosis factor-alpha (TNF-α) inhibitors are being

considered.[15] Alongside these hormonal-based therapeutic regimens, nonsteroidal anti-inflammatory drugs (eg, ibuprofen and acetaminophen) have been commonly used to manage pain-related symptoms, which predominantly act by inhibiting cyclooxygenase-2 (COX-2) receptors.

H1-antihistamines: general overview and side effects

H1-As, previously referred to as H1-receptor antagonists or H1-receptor blockers, belong to a class of therapeutic agents that block the actions of H1 receptors in the body to down-regulate the proinflammatory pathways. Briefly, H1-As are functionally divided into 2 categories[16]—first generation (G1) and second generation (G2). The predominant distinction between them is that G1 H1-As (eg, triprolidine, hydroxyzine, and ketotifen) can freely cross the blood-brain barrier (BB) and block the histamine-related neurotransmitter action, causing sedation and central nervous system (CNS) effects (eg, impaired memory, cognitive, and psychomotor functions). Furthermore, G1 H1-As have been associated with cardiac toxicity effects (eg, increased risk of QT interval prolongation, tachycardia, and cardiac arrhythmia), other systemic effects (eg, dry mouth, urinary retention, peripheral vasodilatation, and increased appetite), and even risks associated with overdose or abuse (eg, extreme CNS depression, delirium, and coma).[17] In contrast, G2 H1-As (usually metabolites of G1 H1-As, eg, acrivastine, cetirizine, fexofenadine, and loratadine) only have minimal BB crossing and subsequent CNS-related effects and minimal observed cardiac toxicity and overdose-related adverse events.

Correlation-driven opinion on H1-antihistamines as an avenue for endometriosis management

In this section, we put forward the growing perspective of various research studies that highlight the presence of different inflammatory processes within ES pathogenesis. Furthermore, we present mechanisms of action by which H1-As act. By drawing from the commonalities between the ES-specific inflammatory pathways and those that H1-As down-regulate, we present our correlation-driven perspective on the potential avenue for H1-As use in ES management.

Inflammatory pathways in endometriosis pathogenesis

In recent years, ES has been increasingly classed as a chronic inflammatory condition,[18,19] owing to growing evidence of an increased prevalence of proinflammatory processes among patients with ES. For example, peritoneal macrophages of patients with ES have been found to demonstrate enhanced activation of nuclear factor kappa B (NF-κB) pathway,[20,21] and ectopic ES lesions have been shown to demonstrate an elevated expression of intercellular adhesion molecule 1 (ICAM-1)[22,23] and COX-2 receptors.[24,25] In addition, peritoneal fluid of patients with ES have been found to have elevated proinflammatory cytokine levels of TNF-α,[1,26] and such elevations have been associated with potentiating a sustained ES.[27] Furthermore, an increased incidence of activated and degranulated mast cells has been found in ES lesions.[28,29] Cytokines (TNF-α, interleukin 6, and interleukin 1β), transcription factors (NF-κB), and prostaglandins (prostaglandin E2) are some of the candidate factors that have been found to promote local estrogen availability within the ES lesion microenvironment and promote its growth.[3] This highlights the intimate connection among the inflammatory mediators, estrogen synthesis and availability, and immune cells in the growth and progression of endometriotic lesions.

Mechanism of action and current usage of H1-antihistamines

Research has revealed that the antiallergenic and anti-inflammatory actions of H1-As are because of various mechanisms, such as inhibition of mediator release via Ca^{+2} channel blocking in mast cells and basophils[30,31] and the down-regulation of the release of proinflammatory cytokines and cellular adhesion molecules (eg, ICAM-1)[32,33] by inhibition of the NF-κB pathway.[34] As such, G2 H1-As have been one of the most widely used and recommended choices of medications for the management and prevention of allergy-related rhinitis, conjunctivitis, and urticaria.[16] Their use outside of these conditions, such as in respiratory conditions (eg, asthma), dermatologic disorders (eg, atopic dermatitis), and CNS diseases (especially G1 H1-As; for anxiety and perioperative sedation), has been considered, although their use has not been officially recommended because of the lack of evidence from large-scale randomized trails.[16,17]

An opinion on H1-antihistamines as a potential avenue for endometriosis management

By viewing the inflammation-driven perspective of ES pathogenesis (§ 3.1) and mechanism of action of commonly used H1-As (§ 3.2), a correlative picture emerges where some of the key inflammatory pathways evidenced to be playing a role in growth and proliferation of ES implants are the same ones that H1-As counteract. As such, the following question emerges: "Can we consider the long-term use of oral H1-As (either G1 or G2) as an avenue for ES management?" The current literature on the direct use of H1-As in ES has been sparse or limited to animal-based studies (eg, the use of ketotifen [a G1 H1-As] on rodents with induced ES).[35] Therefore, there is a strong need to further investigate the potential role of H1-As use for ES management.

In this perspective opinion essay, we recommend that the research community consider H1-As, along with other established hormone regulatory modalities, as a potential therapeutic avenue for ES and its associated symptoms. We have outlined some important questions as a potential guide for future investigations into this topic:

1. How much symptomatic relief (pain and psychological factors) is achieved when using H1-As in patients with ES compared with using NSAID only?
2. Does the down-regulated inflammatory response through the use of

long-term H1-As in patients with ES reduce the amount of active disease?
3. Does postsurgery usage of H1-As in addition to other hormonal therapies reduce the incidence of recurrent ES more than using hormonal therapy alone?

Given that several H1-As are widely available for over-the-counter use and have good worldwide distribution, this new potential therapeutic avenue of H1-As for ES management can be very easily accessible and cheap. However, it is worth keeping in mind the side effects and H1-As's potentiality for adverse events (especially in the case of G1 and, if any, in the case of G2). As such, simultaneous studies into dose-dependent pharmacokinetics and long-term use −related effects of H1-As should be considered and prioritized. Furthermore, it is necessary to establish any contraindication of their use, such as in individuals with hepatic or renal impairment, or cardiac arrhythmic potential. ■

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