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Review

Effect of menopause hormone therapy on disease progression in systemic lupus erythematosus: A systematic review

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ABSTRACT

Objective: To review the literature pertaining to the effect of postmenopausal hormone therapy on disease progression in women with systemic lupus erythematosus.
Methods: We performed a systematic review using PubMed, Embase, and the Cochrane Central Register of Controlled Trials from January 1990 to December 2013 for observational studies and randomized clinical trials that study the effect of hormone therapy on the occurrence of flares in menopausal patients with systemic lupus erythematosus. The screenings of titles and abstracts, full text review, and risk of bias assessments were done by two independent reviewers.
Results: A total of 12,548 articles were identified. After title and abstract screening and removal of duplicates, 692 articles were retrieved for full text review. Five studies were deemed eligible for inclusion in the analysis, and the methodological quality was assessed. Two of the studies were randomized controlled trials and three were observational studies. One randomized controlled trial found that menopausal women who received hormone therapy were at a higher risk for developing minor to moderate flares of systemic lupus erythematosus. In the other four studies, there was no significant difference in systemic lupus erythematosus disease activity between hormone therapy and non-hormone therapy users.
Conclusions: Hormone therapy in menopausal patients with systemic lupus erythematosus appears to be well tolerated. While there is some evidence supporting an increase in risk of mild to moderate flares among hormone therapy users, no association was identified between hormone therapy use and severe disease flares. In addition, hormone therapy was associated with significant improvement in menopausal symptoms and quality of life. Larger trials are required to assess the long-term effects of hormone therapy on the course of systemic lupus erythematosus in menopausal patients and to identify patient characteristics associated with an increased risk of flares in the setting of hormone therapy exposure.

Abbreviations: SLE, systemic lupus erythematosus; HT, hormone therapy; VTE, venous thromboembolism; DHEA, didehydroepiandrosterone; SLE-DAI, systemic lupus erythematous disease activity index; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate; ESR, erythrocyte sedimentation rate.

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Contents

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology. The disease has a high prevalence in females, which suggests that there may be intrinsic factors in females that affect the development and pathophysiology of the disease. The exact prevalence of the disease is variable due to differences in the disease burden worldwide [1–4]. In the United States, the incidence of the disease is 5.7 per 100,000 among Caucasians and 19.2 per 100,000 in African American women in the age group 20–39 [5]. Women with SLE are prone to developing premature ovarian failure due to the use of cyclophosphamide (used in severe cases) [6] and may enter menopause at a younger age. In one study, the median age of entering menopause in SLE patients was 3 years earlier than in controls [7]. In addition, SLE patients are at an increased risk of osteoporosis secondary to prolonged steroid use [8–10].

Hormone therapy (HT) has been shown to be beneficial in preventing bone loss and osteoporotic fractures associated with menopause [11,12]. However, HT is also associated with an increased risk of venous thromboembolism (VTE) and cerebrovascular thrombosis [13]. There is also an increased risk of VTE in patients with SLE who have anti-phospholipid antibodies [14–16]. Combining the risk of HT use with the already existing risk of thrombosis in SLE may deter physicians from prescribing HT to these patients. HT has been found effective in reducing the vasomotor symptoms in women with SLE [17]. However, there is concern that exogenous estrogen could lead to increased SLE disease activity as previous studies have reported exacerbation of SLE during pregnancy [18–20]. A recent systematic review reported that the use of combined oral contraceptive pills did not worsen disease activity in SLE patients with stable or inactive disease [21].

The current recommendation by The North American Menopause Society is to use the lowest effective dose of HT for the shortest period of time for the relief of menopausal symptoms only and not for the primary prevention of disease [22]. However, the question remains whether this lowest dose of HT is safe to use in patients with SLE or whether SLE should be considered an absolute contraindication to HT. The aim of this review is to present a thorough systematic review on the effects of HT on disease progression in SLE patients.

2. Methods

2.1. Data sources and search strategy

The following databases were searched for peer-reviewed articles from 1990 to December 2013: Pubmed, Embase, and the Cochrane Central Register of Controlled Trials. Key terms, MeSH terms, and Embase terms were used in a search strategy created by the help of a librarian. These key words included: *menopause*, *hormone therapy*, and *systemic lupus erythematosus*. Bibliographies of key articles were cross referenced to identify additional relevant publications.

2.2. Study selection

The titles and abstracts were divided into sections, and each section was screened by two independent reviewers (Khafagy and Shen). If either reviewer identified a study as being potentially eligible, the full-text article was retrieved for review. The full text screening was performed by two independent reviewers to determine eligibility. Studies included in this review were limited to those published in English. Case reports were excluded. The predetermined criteria for inclusion of studies were: randomized clinical trials or observational studies comparing women with SLE who received HT, to women with SLE who did not receive HT. HT included compounds that contained estrogen and/or progestogen in any dose, any route of administration, and any duration of exposure. Tibolone was not included as it is not approved for use in the United States. The use of didehydroepiandrosterone (DHEA) was not considered an exposure of interest. The primary outcome of interest was development of minor or major flares knowing a priori that the definition of flare will vary among different studies. We considered minor to moderate flares to be worsening of rash, development of fever, ulcers, or arthritis. Severe flares were considered to involve the central nervous system, thrombocytopenia, vasculitis, or glomerulonephritis. Secondary outcomes included change in the systemic lupus erythematous disease activity index (SLE-DAI) [23]; a validated disease activity measure, hospitalization, or change in medications by increasing current medication dose or adding new medication.

2.3. Risk of bias assessment

Two independent reviewers performed quality assessment of the included studies using the Cochrane risk of bias tool for randomized clinical trials. Quality indicators included adequacy of sequence generation, allocation concealment, subject blinding, personnel and outcome assessors, selective outcome reporting, and extent of loss to follow-up. For observational studies, a form was created to assess sources of selection bias, measurement bias, attrition bias, and reporting bias. Definitions were created to define low-risk and high-risk of bias. Any disagreement was resolved through discussion.