Atherosclerosis 242 (2015) 87–96

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Tibolone decreases Lipoprotein(a) levels in postmenopausal women: A systematic review and meta-analysis of 12 studies with 1009 patients

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ARTICLE INFO

Article history:
Received 28 May 2015
Received in revised form
28 June 2015
Accepted 29 June 2015
Available online 2 July 2015

Keywords:
Cardiovascular disease
Cardiovascular risk
Lipoprotein(a)
Tibolone

ABSTRACT

Introduction: Circulating lipoprotein (a) (Lp(a)) is a recognized risk factor for cardiovascular disease (CVD). Tibolone, a synthetic steroid, may lower Lp(a) levels; however, evidence of the effects of tibolone on Lp(a) still remain to be defined. Therefore, we investigated the effects of tibolone treatment on circulating Lp(a) levels in postmenopausal women.

Methods: The search included PUBMED, Web of Science, Scopus, and Google Scholar (up to January 31st, 2015) to identify controlled clinical studies investigating the effects of oral tibolone treatment on Lp(a) levels in postmenopausal women. Random-effects meta-regression was performed using unrestricted maximum likelihood method for the association between calculated weighted mean difference (WMD) and potential moderators.

Results: Meta-analysis of data from 12 trials (16 treatment arms) suggested a significant reduction of Lp(a) levels following tibolone treatment (WMD: −25.28%, 95% confidence interval [CI]: −36.50, −14.06; $p < 0.001$). This result was robust in the sensitivity analysis and its significance was not influenced after omitting each of the included studies from the meta-analysis. When the studies were categorized according to the tibolone dose, there were consistent significant reductions of Lp(a) in the subsets of studies with doses <2.5 mg/day (WMD: −17.00%, 95%CI: −30.22, −3.77; $p < 0.012$) and 2.5 mg/day (WMD: −29.18%, 95%CI: −45.02, −13.33; $p < 0.001$). Likewise, there were similar reductions in the subsets of trials with follow-up either <24 months (WMD: −26.79%, 95%CI: −38.40, −15.17; $p < 0.001$) or ≥24 months (WMD: −23.10%, 95%CI: −40.17, −6.03; $p = 0.008$).

Conclusions: This meta-analysis shows that oral tibolone treatment significantly lowers circulating Lp(a) levels in postmenopausal women. Further studies are warranted to explore the mechanism of this effect

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.06.056

and the potential value and place of tibolone or its analogues in the treatment of elevated Lp(a) in individuals at risk of CVD.

1. Introduction

Lipoprotein(a) (Lp(a)) is a unique lipoprotein particle, which consists of an apolipoprotein B containing lipoprotein moiety very similar to low-density lipoprotein (LDL) covalently linked to the glycoprotein component apoprotein(a) [apo(a)] [1]. Apo(a) is exclusively produced in the liver, and its secretions highly correlated with circulating Lp(a) levels [2]. Clinical and epidemiological evidence reveals an increased level of Lp(a) to be a causal, independent risk factor for cardiovascular disease (CVD) [3–6]. The atherogenic properties of Lp(a) are associated with several mechanisms, including the inhibition of the fibrinolitic system by homologous structure of apo(a) with plasminogen [7], the interaction with extracellular matrix conjugates such as glycoproteins [8], the binding to scavenger receptors on macrophages [9,10], and the induction of inflammatory molecules [11].

Given the above, there has been an interest in Lp(a) as a target for residual risk therapy [12–14]. In general, circulating Lp(a) levels are genetically determined [15], while the levels can change in certain circumstances, such as under acute vascular and inflammatory pathologies [16–18]. The European Atherosclerosis Society (EAS) Consensus Panel recommends screening for elevated Lp(a) in those at intermediate or high CVD/coronary heart disease (CHD) risk, a desirable level <50 mg/dL as a function of global CV risk, and use of niacin for Lp(a) and CVD/CHD risk reduction [19]. Since currently available LDL cholesterol-lowering drugs, such as statins, have little effects of Lp(a), and other, such as niacin is poorly tolerated and is not available in many countries, there has been a continuous search for effective agents for lowering circulating Lp(a) levels [20].

Tibolone (Livial, Org OD 14) is a synthetic steroid with estrogenic, androgenic and progestogenic properties, and used orally for the prevention of osteoporotic bone loss and hormonal replacement treatment on climacteric symptoms in postmenopausal women [21,22]. Tibolone itself has no activities, but two estrogenic metabolites (3α- and 3β-hydroxy [OH] tibolone) and the third metabolite (Δ4-tibolone) exert the effects on climacteric symptoms, and the third metabolite also exerts additional progestogenic effects in endometrium [23,24]. Tibolone treatment can modulate the lipid profile and its possible reduction of Lp(a) has been observed [25], although the effects of tibolone on Lp(a) were not previously analyzed within systematic review and meta-analysis [22]. Therefore, we performed a meta-analysis to evaluate the efficacy of tibolone treatment on circulating Lp(a) levels in postmenopausal women.

2. Material and methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [26]. PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Web of Science (http://apps.webofknowledge.com), SCOPUS (http://www.scopus.com), and Google Scholar (http://www.scholar.google.com) databases were searcher and the search was limited to the controlled studies (mainly randomized controlled trials [RCTs], as well as controlled clinical trials, perspective and open-label studies) carried out up to January 31, 2014, investigating the potential effects of tibolone treatment on Lp(a) concentrations in the group of postmenopausal women. The databases were searched using the following search terms in titles and abstracts (also in the combination with MESH terms): (tibolone OR OrgOD14 OR "Org OD14" OR livial OR livial®) AND (lipoprotein(a) OR "lipoprotein (a)" OR Lp(a) OR "Lp(a)"). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in humans. Selected articles were searched to identify further relevant studies. Two reviewers (KK and AS) evaluated each article separately. Disagreements were resolved by agreement and discussion with a third party (MB).

2.2. Study selection

Original studies (all in postmenopausal women) were included if they met the following inclusion criteria: (i) being a controlled clinical study (RCT, controlled perspective or open-label study), (ii) investigating the impact of tibolone on plasma/serum concentrations of Lp(a), (iii) presentation of sufficient information on Lp(a) concentrations at baseline and at the end of follow-up in each group or providing the net change values.

Exclusion criteria were: (i) lack of an appropriate control group in the study design, (ii) non-clinical observational studies with case–control, cross-sectional or cohort design, (iii) lack of sufficient information on baseline or follow-up Lp(a) concentrations, (iv) inability to obtain adequate details of study methodology or results from the article or the investigators, and, (v) the study was ongoing.

2.3. Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) study design; 5) tibolone dose and the route of administration; 6) number of participants in the tibolone and control groups; 7) inclusion and exclusion criteria; 8) age, gender and body mass index (BMI) of study participants; 9) prevalence of diabetes mellitus; and 10) baseline and follow-up plasma concentrations of Lp(a).

2.4. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [27]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias. Labeling an item as "unclear" indicated an unclear or unknown risk of bias.

2.5. Quantitative data synthesis

Meta-analysis was conducted using Comprehensive Meta-