Biomedicine & Pharmacotherapy 106 (2018) 956–965

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

# Potential role of leukotriene receptor antagonists in reducing cardiovascular and cerbrovascular risk: A systematic review of human clinical trials and *in vivo* animal studies

Malvina Hoxha[a,b,*], Anne-Mary Lewis-Mikhael[c], Aurora Bueno-Cavanillas[d,e,f]

[a] Catholic University Our Lady of Good Counsel, Department of Chemical- Toxicological and Pharmacological Evaluation of Drugs, Rruga Dritan Hoxha, Tirana, Albania
[b] Università degli studi di Milano, Department of Pharmacological and Biomolecular Sciences, Via Balzaretti, 9-20133, Milan, Italy
[c] McMaster University, Hamilton, Ontario, Canada
[d] Department of Preventive Medicine and Public Health, University of Granada, Spain
[e] Instituto de Investigación Biosantiaria, IBS Granada, Spain
[f] Ciber of Epidemiology and Public Health (CIBERESP), Spain

ARTICLE INFO

*Keywords:*
Leukotriene receptor antagonist
Montelukast
Cardiovascular event
Cysteinyl leukotrienes
Ischemic stroke

ABSTRACT

*Background:* Leukotrienes are important lipid mediators of inflammation arising from arachidonic acid cascade. They are implicated in vascular inflammation and produced in different pathologic conditions as atherosclerosis, stroke and myocardial infarction. Different studies have investigated the role of leukotriene receptor antagonist (LTRA) in reducing some cardiovascular events, especially in animals. We conducted a systematic review of both *in vivo* animal and human studies to determine the potential role of leukotriene receptor antagonist in reducing cardiovascular and cerebrovascular events.

*Methods: Data sources*: Pubmed, Embase and Cochrane database. *Data extraction*: Two reviewers independently screened potentially eligible articles and extracted relevant data.

*Results:* A total of 28 studies were included, of which 26 were conducted in animals, and 2 in humans.

*Conclusions:* All animal studies reported that using a leukotriene receptor antagonist brings to a reduction of either myocardial infarction, ischemic stroke, or atherosclerosis risk. Similar results were obtained from two clinical trials on humans, suggesting a potential role of montelukast in reducing some cardiovascular diseases.

## 1. Introduction

Leukotrienes are arachidonic acid (AA) mediators implicated in inflammation, particularly vascular inflammation that takes place in different cardiovascular (CV) events including myocardial infarction, atherosclerosis and stroke. They are classified in two groups: $LTB_4$ and cysteinyl leukotrienes (CysLTs: leukotriene C(4), D(4), E(4)) based on the absence/presence of a cysteinyl group respectively (Fig. 1). CysLTs are concerned primarily with inflammation by increasing the capillary permeability and acting as vasoconstrictors. They are also involved in hypertension and thus enhance cardiovascular risk [1,2]. CysLT1R and CysLT2R are the two G-protein coupled receptors of the CysLTs [3] that are found in injured human arteries [4,5].

Montelukast, zafirlukast, pranlukast and pobilukast were the first leukotriene receptor antagonists (LTRA) and selective inhibitors of CysLT1 receptor that were approved for use in asthmatic patients [6,7], and later on for the treatment of allergic rhinitis and urticaria [8]. In experimental models (*in vivo),* they have demonstrated to play a role in reducing the blood-brain barrier permeability and brain injuries [9–12]. Different studies conducted on animals using a LTRA have reported their potential role in reducing the risk of cardiovascular disease. Ge S. et al have shown that montelukast had antiatherogenic effects in rabbit carotid injury [13]. Mueller CF found that montelukast ameliorates the atherosclerotic plaque generation [14], while B a¨ck M provided evidence that montelukast reduces the expression of matrix metalloproteinases (MMP-2 and MMP-9) preventing progression of atherosclerosis [15]. In line with these findings, other *in vivo* studies on mice reported the role of LRA, specifically montelukast, in improving

*Abbreviations:* AA, arachidonic acid; CV, Cardiovascular; CysLTs, cysteinyl leukotrienes; CysLTR, cysteinyl leukotrienes receptor; LT, leukotrienes; LTRA, leukotrienes receptor antagonist

* Corresponding author at: Catholic University Our Lady of Good Counsel, Department of Chemical- Toxicological and Pharmacological Evaluation of Drugs, Rruga Dritan Hoxha, Tirana, Albania.

*E-mail addresses:* m.hoxha@unizkm.al, malvis22@hotmail.com (M. Hoxha).

https://doi.org/10.1016/j.biopha.2018.07.033
Received 23 February 2018; Received in revised form 6 July 2018; Accepted 6 July 2018

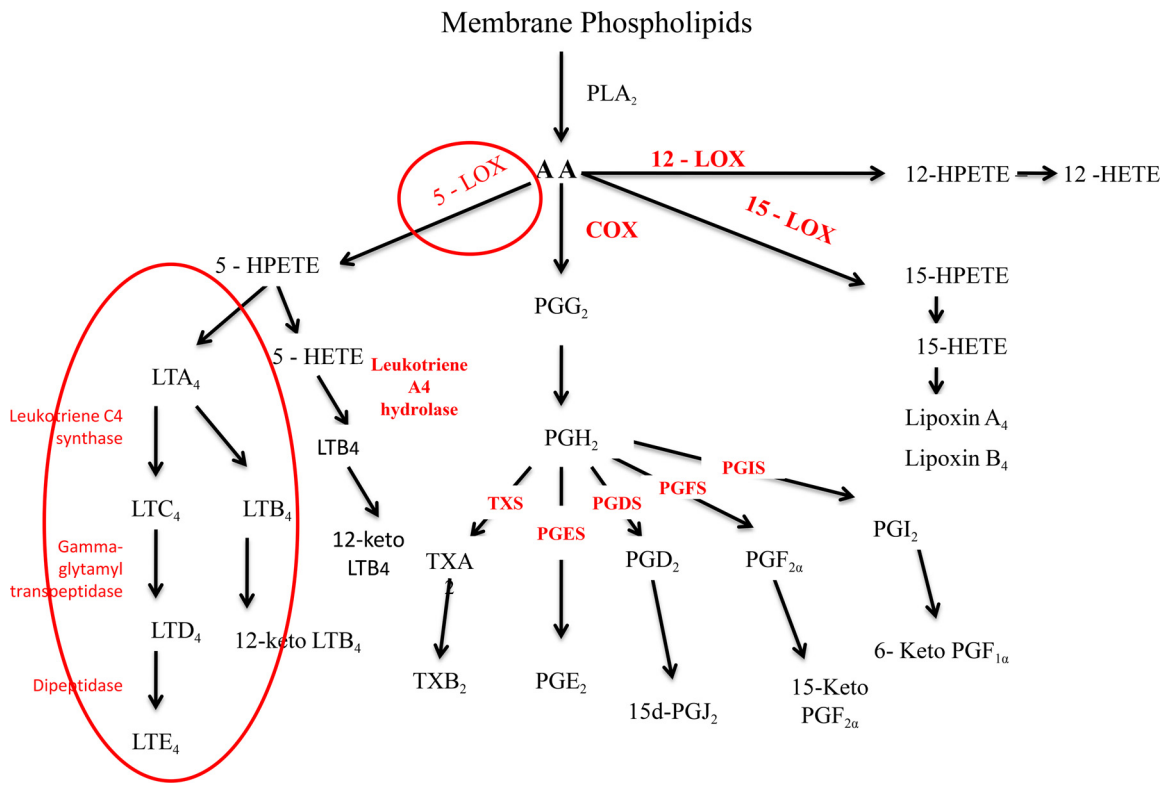


**Fig. 1.** Arachidonic acid pathway and 5-LO pathway.
Arachidonic acid gives rise to several metabolites. Prostaglandins and thromboxane are produced *via* the COX-pathway, unlike leukotrienes that are produced *via* 5-LO pathway. Leukotrienes are classified in leukotrienes (LTB4) and cysteinyl leukotrienes (CysLT: LTC4, LTD4, LTE4). 5-LO pathway is marked with red in the Figure. Abbreviations: phospholipase $A_2$ ($PLA_2$), arachidonic acid (AA), 5-lipoxygenase (5-LO), 15-Lipoxygenase (15-LO), 12-lipoxygenase (12-LOX), cyclooxygenase (COX), Prostaglandin $G_2$ ($PGG_2$), Prostaglandin $H_2$ ($PGH_2$), thromboxane synthase (TXS), thromboxane $A_2$ ($TXA_2$), thromboxane $B_2$ ($TXB_2$), Prostaglandin E synthase (PGES), Prostaglandin $E_2$ ($PGE_2$), Prostaglandin D synthase (PGDS), Prostaglandin $D_2$ ($PGD_2$), 15-deoxy-D12,14-prostaglandin $J_2$ (15d-$PGJ_2$), Prostaglandin F synthase (PGFS), Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), 15-keto Prostaglandin $F_{2\alpha}$ (15-keto $PGF_{2\alpha}$), Prostaglandin I synthase (PGIS), Prostacyclin ($PGI_2$), 6-keto Prostaglandin $F_{1\alpha}$ (6-keto $PGF_{1\alpha}$), 15-hydroperoxyeicosatetraenoic (15-HPETE), 15- hydroxyeicosatetraenoic acid (15-HETE), 12-hydroperoxyeicosatetraenoic (12-HPETE), 12- hydroxyeicosatetraenoic acid (12-HETE), 5-hydroperoxyeicosatetraenoic (5-HPETE), 5- hydroxyeicosatetraenoic acid (5-HETE), leukotriene $A_4$ ($LTA_4$), leukotriene $B_4$ ($LTB_4$), leukotriene $C_4$ ($LTC_4$), leukotriene $D_4$ ($LTD_4$), leukotriene $E_4$ ($LTE_4$), 12-keto leukotriene $B_4$ (12-keto $LTB_4$).

the endothelial-cell function by reducing the vascular reactive oxygen species production and thus diminishing the atherosclerotic damaged areas [16,17]. This is in addition to its protective role in cerebral ischemia [18] through the same mechanisms.

On the other hand, human experimental studies have also been conducted to examine the role of LRA in CV diseases. Ingelsson et al. reported that montelukast might have a potential role for secondary prevention of CV disease. The results demonstrated a reduction in the risk for recurrent myocardial infarction in male subjects (HR, 0.65; 95% CI, 0.43–0.99), as well as recurrent stroke (HR, 0.62; 95% CI, 0.38–0.99) in patients taking montelukast [19]. This study was conducted in Sweden with a follow up period of three years. These findings prompted the authors to hypothesize a potential interaction of montelukast with the CysLT2 receptors, despite being a selective CysLT1 inhibitor.

Accordingly, LTRAs might have a protective role in the CV and cerebrovascular events through their antiapoptotic and anti-inflammatory functions [20]. The objective of this systematic review is to evaluate the available literature of *in vivo* animal studies and human clinical trials on the potential association between using LTRA and the reduction of the CV and cerebrovascular events.

## 2. Research methods and reporting

This systematic review was conducted according to the preferred reporting items for systematic reviews (PRISMA) guidelines [21]. We collected all the relevant data conformed to the eligibility criteria and answered our research question: Do LTRAs reduce CV and cerebrovascular events?

### 2.1. Study design

Based on previous published evidence of CysLTs involvement in atherosclerosis and ischemia [22,23], we conducted a systematic review to assess the role of LTRA in reducing CV and cerebral events in both animal studies and human clinical trials.

Despite our enthusiasm to conduct a meta-analysis of the data published on this novel topic, it was not possible due to data insufficiency. We contacted several authors to obtain relevant data, but only one responded.

### 2.2. Eligibility criteria

Predefined eligibility criteria for inclusion of the studies were as follows: All published Randomized Controlled Trials (RCTs) or observational studies (cohort or case control design) dealing with the association between LTRA and CV and cerebrovascular events. The following events were considered as primary effects: ischemic stroke, myocardial infarction, atherosclerosis progression, brain injury and infarct size. Secondary outcomes included: reduction of CV risk factors as blood pressure, inflammatory biomarkers and lipid levels of CV diseases, neurological deficit scores, neuron density and inflammatory markers.

Our search was not restricted by year of publication or age of the