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REVIEW

The leukotriene receptor antagonist montelukast and its possible role in the cardiovascular field

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Abstract
Background Cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are pro-inflammatory mediators of the 5-lipooxygenase (5-LO) pathway, that play an important role in bronchoconstriction, but can also enhance endothelial cell permeability and myocardial contractility, and are involved in many other inflammatory conditions. In the late 1990s, leukotriene receptor antagonists (LTRAs) were introduced in therapy for asthma and later on, approved for the relief of the symptoms of allergic rhinitis, chronic obstructive pulmonary disease, and urticaria. In addition, it has been shown that LTRAs may have a potential role in preventing atherosclerosis progression.
Purpose The aims of this short review are to delineate the potential cardiovascular protective role of a LTRA, montelukast, beyond its traditional use, and to foster the design of appropriate clinical trials to test this hypothesis.
Results and Conclusions

What it is known about leukotriene receptor antagonists?
- Leukotriene receptor antagonist, such as montelukast and zafirlukast, is used in asthma, COPD, and allergic rhinitis.
- Montelukast is the most prescribed $CysLT_1$ antagonist used in asthmatic patients.
- Different in vivo animal studies have shown that leukotriene receptor antagonists can prevent the atherosclerosis progression, and have a protective role after cerebral ischemia.

What we still need to know?
- Today, there is a need for conducting clinical trials to assess the role of montelukast in reducing cardiovascular risk and to further understand the mechanism of action behind this effect.

Keywords Leukotrienes · Cardiovascular disease · Leukotriene receptor antagonists · Montelukast

Arachidonic acid pathway

Arachidonic acid (AA) (5, 8, 11, 14-eicosatetraenoic acid) is a polyunsaturated fatty acid, abundant in cell membrane phospholipids and mainly released upon activation of cytosolic phospholipase A_2 ($cPLA_2$). Soon after its release, AA is further metabolized by several enzymatic and non-enzymatic pathways, such as cyclooxygenase (COX) and lipoxygenase (LOX) pathways.

The COX enzyme, also known as PGH synthase (PGHS), gives rise to the production of cyclic endoperoxides (PGG_2-PGH_2), hence to different prostaglandins (PGs), i.e., PGD_2, PGE_2, $PGF_{2\alpha}$, and prostacyclin (PGI_2), and thromboxane (TXA_2). Two isoforms of this enzyme have been identified [1]: COX-1, the constitutive isoform, involved in various processes such as thromboxane synthesis in platelets, PGI_2 production in vascular endothelium, and prostanoid generation at

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gastric mucosal level. COX-2 [2, 3], on the other hand, is the inducible isoform involved in various processes, particularly inflammation. It is expressed in response to pro-inflammatory stimuli (different traumas, heat, cytokines, etc.), causing an increase synthesis of prostanoids that contribute to the classical signs and symptoms of the inflammatory process [4].

Arachidonic acid and 5-lipooxygenase pathway

LOXs are a group of enzymes that metabolize AA into monohydroxylated products, namely hydroperoxyeicosatetraenoic acid (HPETE). These enzymes are classified as 5-LO, 12-LO, and 15-LO according to the site of hydroperoxy group insertion [5].

The 5-LO pathway gives rise, mainly, to the production of leukotrienes (LTs). LTs may be classified in two groups: the dihydroxy acid, represented by leukotriene B_4 (LTB_4), and peptide leukotrienes or cysteinyl leukotrienes (cysteinyl-LTs) (Fig. 1). LTB_4 exerts its action through binding to two officially recognized GPCRs, BLT_1 (expressed in leukocytes and monocytes) and BLT_2 [6–8], while cysteinyl-LTs bind to $CysLT_1$ and $CysLT_2$ receptors [7–9]. $CysLT_1$ and $CysLT_2$ are also GPCRs that share only a 38% amino acid identity and that are expressed by the cells of the immune system, (B cells, T cells, macrophages, monocytes, etc.) [10], by vascular smooth muscle (SMCs), and by endothelial cells (ECs) [11].

LTs are responsible for a series of activities such as contraction of bronchial SMC, accumulation of leukocytes at the inflammatory sites, increase in permeability of postcapillary venules, and the formation of edema [7]. In particular, a number of reviews highlight that cysteinyl-LTs, (LTC_4, LTD_4, and LTE_4), besides their preeminent role in asthma and in inflammation [11, 12], can also enhance the cardiovascular (CV) risk [13–16]; they are, indeed, important mediators of the inflammatory process that characterize several CV pathologies [17]. Over the years, cysteinyl-LTs have been demonstrated to be a potent coronary artery vasoconstrictor [18], to stimulate proliferation of arterial SMCs [19], and to increase platelet-activating factor (PAF) synthesis [20], von Willebrand factor secretion [21], and P-selectin surface expression [22] in cultured ECs.

Myocardial infarction (MI), stroke, atherosclerosis, and aortic aneurysms are some of the CV events characterized by an increase generation of LTs. Urinary excretion of LTE_4 has been reported to be increased in patients with cardiac ischemia [23, 24], as well as in coronary artery disease and after coronary artery bypass surgery [25], or in the urine of rabbits after coronary artery ligation [26]. In addition, transcellular biosynthesis of LTs takes place when neutrophils adhere to coronary ECs and, following activation, induce formation of cysteinyl-LTs and a slow increase in coronary tone and vascular edema responsible of cardiac damage [27, 28]. Interestingly, two human genetic studies have correlated polymorphism of the 5-LO pathway with relative risk for MI, stroke, and atherosclerosis focusing attention to LTs in the pathogenesis of these diseases [29, 30].

A first report on targeted gene disruption reveals the role of $CysLT_1$ in the enhanced vascular permeability of mice

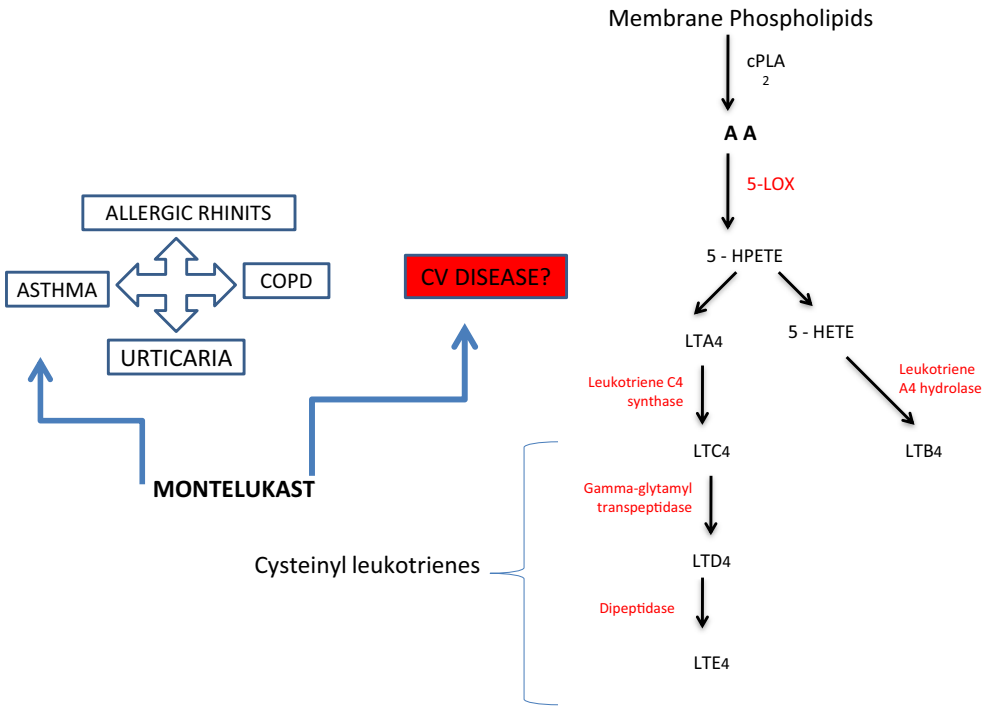

Fig. 1 5-LO pathway. Leukotrienes are produced via 5-LO pathway. They are classified in leukotriene B_4 (LTB_4) and cysteinyl leukotrienes (cysteinyl-LTs: LTC_4, LTD_4, LTE_4). Abbreviations: *cPLA*$_2$ cytosolic phospholipase A_2, *AA* arachidonic acid, *5-LO* 5-lipoxygenase, *5-HPETE* 5-hydroperoxyeicosatetraenoic, *5-HETE* 5- hydroxyeicosatetraenoic acid, *LTA*$_4$ leukotriene A_4, *LTB*$_4$ leukotriene B_4, *LTC*$_4$ leukotriene C_4, *LTD*$_4$ leukotriene D_4, *LTE*$_4$ leukotriene E_4

undergoing acute inflammatory responses [31], while transcripts of FLAP and LT receptors have been identified in specimens of arterial walls of patients affected by atherosclerosis of the aorta and of coronary and carotid arteries [32]. More recently, $CysLT_1$ receptor expression in human aortic valve myofibroblasts has been demonstrated to correlate with severity of stenosis [33], while lipopolysaccharide stimulation induces its perinuclear expression in human coronary artery vascular SMCs, a localization that correlates with an increase in mRNA levels for plasminogen activator inhibitor (PAI)-2, a well-known pro-atherosclerotic gene [34].

In addition, cysteinyl-LTs have been also associated with neuronal injury after brain ischemia [35, 36], apparently through the activation of both $CysLT_1$ and $CysLT_2$ receptors [37–40].

Thus, a number of studies reported that cysteinyl-LTs and their receptors play a prominent role in the increase of vasoconstriction, reduction of coronary blood flow, atherosclerosis, hypertension, myocardial ischemia, and stroke [17, 41–45].

Leukotriene modifiers

After vast evidences that cysteinyl-LTs are correlated with the pathophysiology of asthma and allergic rhinitis (AR) [46–50], leukotriene receptor antagonists (LTRAs) were developed in the late 1990s and were approved for the use in asthmatic patient [51–58]. The first LTRAs developed, i.e., montelukast, pranlukast, zafirlukast, and pobilukast are, mainly, inhibitors of $CysLT_1$ receptor [59], while newer compounds are either non selective inhibitor of both $CysLT_1$ and $CysLT_2$ (BAY u9773) [60, 61], or more selective inhibitors of $CysLT_2$ (Bay $CysLT_2$ [62, 63] and HAMI 3379 [64]).

While it is not been approved by EMA (European Medicines Agency), the 5-LO inhibitor zileuton is on the market in the USA for the treatment of asthma. However, 4.6% of patients receiving zileuton had serum alanine transaminase elevations [65], and this side effect combined with a relatively low potency of the drug and its unfavorable therapeutic regimen has limited its use in the clinical practice.

However, 5-LO and FLAP inhibitors, due to their broader pharmacological profile, have been tested in animal models of CV diseases, with varied results. Indeed, significant reduction of infarct size, inflammation, atherosclerotic lesion, and intima-media thickness has been observed with some of these compounds [28, 66–72], while the 5-LO inhibitor and LTRA REV-5901 [73] failed to reduce the extent of MI size following occlusion-reperfusion injury [74]. Furthermore, studies using 5-LO-deficient mice did not reveal any difference in MI area or atherosclerosis vs. controls [75, 76], while two 5-LO inhibitors showed opposite effects in $apoE^{-/-}$ [77] and in $LDLR^{-/-}$ mice [78].

A prospective clinical trial with DG-031 conducted in patients with the at-risk variants of FLAP and LTA_4-H showed a significant reduction of biomarkers associated with increased risk of MI [79]. More recently, in two small clinical trials in patient with recent acute coronary syndrome, reduction in non-calcified plaque volume [80] and a slower plaque progression [81] have been observed with the new 5-LO inhibitor VIA-2291 (atreleuton), proving that a reduction in LT production may influence atherosclerosis in humans.

However, 5-LO inhibition will also cause inhibition of specialized pro-resolving lipid mediators such as lipoxin (LXs) and resolvins [82], which may contribute to the resolution of the inflammatory process at the base of many cardiovascular diseases [83, 84]. For example, CGEN-855A, an ALX/FPR2 peptide agonist, provided protection against ischemia-reperfusion injury through inhibition of PMN recruitment to the myocardium [85]. Furthermore, an epi-lipoxin stable analogs inhibited human EC proliferation and migration [86], while inducing protection against pro-oxidant insults [87] and suppression of NAD(P)H oxidase-mediated ROS generation [88], strongly indicating that LXs may play a protective role against the development and progression of CVDs. In addition, resolving E1 (RvE1) has been demonstrated to reduce ADP-stimulated P-selectin mobilization and actin polymerization and may contribute to both resolution of vascular inflammation and ADP-dependent platelet activation [89]. Taken together, as it is also the case for the COX pathway, these results suggest that altering the equilibrium between pro-inflammatory and anti-inflammatory AA metabolites might not be the most appropriate pharmacological strategy to pursue. Rather, a selective inhibition of a specific target (i.e., receptor), avoiding disruption of the intricate inter-eicosanoid balance and its physiological consequences, should provide additional selectivity to the therapeutic intervention and reduce unwanted side effects [90].

Leukotriene receptor antagonist, montelukast

LTRAs such as montelukast, zafirlukast, or pranlukast can be used in AR [91] or other pathological situations such as urticaria, allergic fungal conjunctivitis, paranasal sinus disease, and atopic dermatitis [58]. In this context, montelukast, a potent antagonist of the $CysLT_1$ receptor subtype, is currently used in patients with different levels of asthma severity or chronic obstructive pulmonary disease (COPD) as an add-on therapy to inhaled corticosteroids. In addition, montelukast alleviates the symptoms present in AR, like eye and throat irritation, and it is commonly prescribed as a monotherapy or in association with antihistamine drugs [92, 93]. Adachi et al. [94] demonstrated an improvement of FEV_1 in acute asthma in patients taking intravenous montelukast compared to placebo, irrespectively of the concurrent use of inhaled

corticosteroids [95]. These results are in line with the Montelukast Asthma Study Group demonstrating an improvement of FEV_1 in patients taking oral or intravenous montelukast compared to placebo [96, 97]. Moreover, data from the Rubeinstein et al. study demonstrated an improvement of nocturnal symptoms, a reduction of the number and duration of hospitalizations, and emergency visit in COPD patients taking montelukast [98], while similar results were also obtained in pulmonary function and quality of life tests [99]. While LTRAs as monotherapy improved asthma control compared with placebo both in adults and children [100] and some recent clinical trials seem to suggest that they are equivalent to an inhaled glucocorticoid as first-line controller therapy at least in the short period [101], the more recent systematic review of randomized clinical trials available concluded that as monotherapy, inhaled corticosteroids display superior efficacy to LTRAs in adults and children with persistent asthma [102]. Montelukast is a well-tolerated anti-asthmatic drug that can also be used in children [103–105] for its anti-inflammatory and bronchoprotective action and is usually administrated in the oral dosage form.

In this context, several studies retain a beneficial effect of montelukast in cystic fibrosis [106, 107] in the respiratory syncitial virus (RSV) bronchiolitis [108], and in the treatment of sepsis [109]. Montelukast and zafirlukast have also been reported to inhibit the activation of NF-κB in a human monocyte/macrophage cell line [110–112].

Montelukast is metabolized by the cytochromes P450, 2C9, and 3A4 in the liver [113]. Currently, no biomarker to assess the response to montelukast exists, considering that a number of patients, particularly children, do not have a better response to montelukast treatment compared to inhaled corticosteroids [114]. Moreover, several studies have reported that even though montelukast is considered as a safe drug, its use is sometimes associated with Churg-Strauss syndrome, depression, suicidal thinking, anxiety, and sleep disturbances [115–118].

In vivo animal studies on the role of montelukast on the cardiovascular disease

Considering the emerging role of cysteinyl-LTs in the pathophysiology of CV disease (CVDs), several studies have been conducted to assess the role of LTRAs in animal models of CVDs.

LTRAs such as montelukast or pranlukast have been shown to have a protective role after cerebral ischemia [15] and reduce the blood-brain barrier permeability as well as brain injuries in several experimental models, in vivo [119–125]. Saad MA. et al.'s findings demonstrated that montelukast had a neuroprotective effect mediated through its antioxidant, antiapoptotic, anti-inflammatory and mechanism, in cerebral ischemia/reperfusion (I/R) injury in rats [126]. In line with that, another study has shown a neuroprotective effect in spinal cord I/R injury in rats treated with montelukast [127]. Indeed, a number of articles have reported the involvement of also $CysLT_2$ in the inflammatory process subsequent to a brain vascular insult [59, 128–130]. In accordance with the previously mentioned results, evidences have been provided of the protective role of HAMI 3379, a selective $CysLT_2$ antagonist, against brain injury after focal cerebral ischemia in rats [131, 132] or in ischemia-like neuronal injury [133].

In addition, in vivo studies in the mouse revealed that montelukast can reduce the production of vascular reactive oxygen species (ROS), improving EC function, inhibiting atherosclerotic damaged area and intimal hyperplasia [134, 135] as well as decreasing atherosclerotic plaque generation [136]. In line with these data, other studies in rabbits indicate that LTRAs can prevent atherosclerosis progression, and that it inhibits neointimal hyperplasia, increases SMC, and decreases macrophage accumulation and the expression of matrix metalloproteinases (MMP-2 and MMP-9), which have an essential role in the development of atherosclerotic plaque [137]. Interestingly, in a rabbit carotid balloon injury model conducted to investigate the effect of montelukast on atherosclerosis compared to atorvastatin, the results indicate no significant differences between the two drugs in reducing neointima and MCP-1 expression. However, atorvastatin reduces also the trigycerides and LDL levels, unlike montelukast, suggesting that montelukast exerts its anti-atherogenic effect through the MCP-1 down regulation [138]. Becher et al. found that the inhibition of LTC_4 activity in mice by montelukast reduces oxidative stress and apoptosis in cardiomyocytes having a beneficial effect on myocardium remodeling after left ventricular injury [139]. In this context, in $apoE^{-/-}$ mice, an attenuated myocardial necrosis area was found after acute hypoxia, suggesting that montelukast exerts a cardio-protective role during myocardial injury likely improving the oxygen supply to areas of myocardial ischemia [140].

Other in vivo animal studies have shown that montelukast can prevent the liver and intestine injury by reducing apoptosis and oxidative stress in a hepatic I/R model [141], can protect against I/R-induced intestinal damage [142, 143] and liver injury in rats improving hepatic structure and function [144], and can prevent damage in a model of colonic anastomotic wound healing [145]. In addition, montelukast has been demonstrated to prevent I/R-induced damage in rat ovary [146, 147] and testis [148], to protect against renal and bladder I/R injury by its anti-inflammatory and antioxidant properties [149, 150], and has been found effective in ameliorating I/R-induced vasculitic neuropathic pain [151], as well as, in association with iloprost, in reducing I/R damage in transient spinal cord ischemia [152].

Complementary studies also conducted in animals making use of other LTRAs such as zafirlukast or pranlukast mostly confirmed the montelukast data. Haga et al. demonstrated that zafirlukast reduces the severity of ischemic acute renal failure, through the anti-inflammatory action [153], while other studies suggested that zafirlukast can be added to combined therapy of necrotic, hypoxic, and ischemic injuries of the myocardium [154]. In addition, De Clue et al. confirmed that zafirlukast ameliorated the acute hypotensive response to endotoxin in cats, but without significant effect in the heart rate and TNF or IL-6 production [155]. These data were also confirmed for another LTRA, pranlukast, which reduced infarct size [156], attenuated hydrogen peroxide-induced necrosis [157] and ischemia-like injury in ECs [158], suggesting that pranlukast can be a potential therapeutic alternative for the treatment of ischemic stroke.

However, some contradictory results have also been published, likely due to the use of old, non-selective, and reduced potency CysLT receptor antagonists (see [45] for a recent review).

Clinical trials on the role of montelukast in the prevention of CV diseases

Taken together, all these in vivo animal data strongly indicate a potential role of montelukast in reducing the CV risk. Regarding the inflammatory response, present not only in pathological situation such as asthma but also in carotid and coronary atherosclerosis, it can be hypothesized that montelukast might be useful to prevent the MI or stroke in humans. However, a very limited number of studies have been conducted in humans to further confirm the results obtained in the animal models.

In support to this hypothesis, Allayee et al. group conducted a clinical trial investigating the role of montelukast and low-dose theophylline on CVD risk factors, such as inflammatory biomarkers and lipid levels. The result demonstrate a reduction of C-reactive protein levels, as well as reduced levels of all lipids such as total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density cholesterol (HDL-C) in patients taking montelukast compared to that in placebo. Despite the reduction of HDL-C levels, the result suggests that the asthmatic patient group taking montelukast has lower levels of CVD-associated inflammatory biomarkers and lipid levels [159]. More recently, Ingelsson et al. conducted a retrospective study in a nationwide population-based cohort of approximately 7 million Swedish hypothesizing that there may be a potential role of montelukast for secondary prevention of CVDs [160]. The cohort consisted of all Swedish residents older than 18 years with a follow-up period from July 1, 2005 to December 31, 2008. Patients were considered exposed when they utilized montelukast for at least 3 continual months. Other dispensed medications, gender, age, comorbidity, and socioeconomic status were also assessed. Montelukast use was analyzed as a time-dependent variable, and the data demonstrated a reduction of the risk for recurrent stroke in patients exposed to the drug (HR, 0.62; 95% CI, 0.38–0.99), accompanied with a lower risk for recurrent MI in male subjects (HR, 0.65; 95% CI, 0.43–0.99). Interestingly, the results demonstrated that only patients not taking angiotensin-converting enzyme (ACE) inhibitors had a decreased risk for recurrent stroke (HR, 0.34; 95% CI, 0.14–0.82) associated to montelukast [160].

Despite that these findings are in line with the protective role of LTRAs obtained in in vivo animal models, additional clinical trials should be performed to confirm this hypothesis and to evaluate the mechanism of action behind this additional role of montelukast. In particular, as the assumption of anti-asthmatic drug is a chronic condition that might continue for the entire life, the time of exposure to LTRAs should be extended.

Final considerations

Inflammation is a key process for the cerebro-vascular diseases, and LTs, important mediators of inflammation, are involved in a variety of inflammatory diseases beyond asthma [5, 11]. In particular, cysteinyl-LTs have been postulated to contribute to CVDs such as atherosclerosis and ischemia [44, 45], inducing the proliferation of endothelial [161] and SMCs [19, 134, 162], thus provoking vasoconstriction and reduction of coronary blood flow. These observations strongly suggest that the anti-inflammatory strategy, and particularly LTRAs, could be effective in treating and preventing atherosclerosis. At present, however, LTRAs in general and montelukast in particular have been approved only for the treatment of asthma and both seasonal and perennial AR [163].

The results obtained in in vivo animal models and in yet limited human clinical trial, however, suggest that montelukast, the most prescribed LTRA, can reduce the risk of CV events. Moreover, these results are in line with the findings from other animal studies using different LTRAs such as pranlukast or zafirlukast. Despite using different animal models such as mice, rats, rabbits, or cats and measuring different parameters, all the studies give evidence of a potential protective role of montelukast with respect to CV and cerebral events through its antiapoptotic and anti-inflammatory activities. Neurological deficit score, infarct volume, brain edema, neuron density, cytokine production, lesion volume, blood pressure, lipid levels, macrophage content, intima thickness, lactate dehydrogenase activity, and oxidative stress biomarkers are some of the parameters measured

in these animal studies to further evaluate the protective effect of LTRAs [164].

Although there are a limited number of studies in humans, Ingelsson's contribution is an important piece of information for further confirmation of this speculation [160]. This, hopefully, can open the way towards other uses of montelukast, beyond its traditional use, which can be especially important for patients with high CV risk factors, considering also that asthmatic patient can have a higher risk for developing CVDs [165]. Montelukast, despite being a highly selective $CysLT_1$ antagonist [59, 62], has a broader spectrum of pharmacological effect in vivo beyond its recognized efficacy in airway diseases [118, 166], while the mechanism behind its cardioprotective effect is not yet known, it can probably can be attributed to its anti-inflammatory activity.

In summary, the results of the current work seem to provide evidences that montelukast can be used to prevent CVDs in humans and inhibit the atherosclerosis development in in vivo animal models. We believe that this postulated beneficial effect of montelukast in the CV system can lead to alternate strategies to treat asthma, COPD, AR, urticaria, or other inflammatory diseases in patients with a high CV risk by using a single drug that will provide an anti-inflammatory and preventing effect also for the CV system.

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