Chinese Journal of Evidence-Based Medicine

BIOLOGICAL ROLE, MECHANISM OF ACTION AND IMPORTANCE OF INTERLEUKIN 1 AND TNF ALPHA IN ASTHMA PATHOGENESIS

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ABSTRACT

In asthmatic patients, the inflammatory responses within the airways are initiated and sustained by different inflammatory mediators or cytokines in which two vital cytokines which are responsible for the pathogenesis of asthma are TNF-α (Tumor Necrosis Factor) and IL (interleukin)-1. The IL-1 aids to the development and progression of asthma by activating dendritic cells responsible for presenting antigens to T cells, and induction of Th2 cells, which produce key cytokines (IL-4, 5, and 13) included in asthma pathogenesis. TNF-α action leads to the development of inflammation by triggering the function of airway epithelium which activates the adhesion molecules and chemokines, which in turn attract and activate immune cells. Furthermore, TNF-α is additionally capable for inducing smooth muscle airway hyperresponsiveness (AHR) by activating ion channels, leading to bronchoconstriction. Importantly, TNF-α is responsible for inducing smooth muscle contractility and airway hyperresponsiveness (AHR), which occurs through ROS (Reactive Oxygen Species) incitement within cells there by activating distinctive signaling pathways, including the RhoA/ROCK pathway, which contributes to airway contraction. Therefore, focusing on the IL-1 and TNF-α pathway has ended up a potential restorative approach for the management of asthma and their wide-ranging effects making them viable interventions requiring for the prospective assessment.

KEYWORDS: Asthma, Biological role, Hyperresponsiveness, Inflammation, Interleukin 1, Tumor Necrosis Factor -α.

INTRODUCTION

Asthma is a chronic disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. Symptoms may occur several times in a day or week in affected individuals and for some people, become worse during physical activity or at night. (1) "Asthma, in medical parlance, is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells." (2) In 2019, an estimated 262 million people worldwide had asthma, representing an increase of 14% since 2006. The occurrence of asthma shows significant variation across different countries and regions, with higher rates observed in wealthier nations as opposed to lower and middle-income countries. (1) Asthma is highly prevalent in children than adults; findings of the Global Report on Asthma 2018, indicate its 11% incidence in children (age range: 2-7 years); however, for adults, its approximately

8%. (3) In India, asthma is a commonly prevalent chronic disease. The disease's overall occurrence in India is estimated to be approximately 2-3%, with a higher incidence rate observed in urban regions (3.3%) as compared to rural areas (2%), as per the reports from Indian Council of Medical Research (ICMR). (4) In 2019, a comprehensive study was carried out, which revealed that the incidence of asthma in India was 2.5%. Furthermore, the study showed its lesser occurrence in males than females (2.2% vs 2.7%). (5) As per the Global Asthma Report of 2018, approximately 400,000 deaths occur annually across the globe due to asthma. The report highlights that asthma claims the lives of 1000 people each day, and a significant number of these deaths can be prevented with appropriate management and care. (3) Data from the study on the global disease burden (2017) revealed a 7.5% attribution of asthma to non-communicable disease-related DALYs lost in India. The actual mortality rate estimation in India is challenging to determine due to inadequate data and under-reporting. (6) The WHO data reveals India's contribution to 10% of asthma-related deaths on a global scale (2016). (7)

Asthma has various risk factors, including genetics, environmental factors like allergen and pollution exposure, and lifestyle factors such as smoking and lack of physical activity. Studies have demonstrated that genetic factors may contribute to up to 60% of the risk of developing asthma. (8) Children, in particular, may develop asthma from viral respiratory infections like the common cold. Additionally, being exposed to certain substances, such as chemicals, dust, and fumes, at work can elevate asthma incidence in children, adults, and the elderly. (9)Asthma control/management requires a combination of preventive measures, including reducing exposure to triggers, using medications, and adopting healthy lifestyle habits.

Pathophysiology of asthma

The respiratory complications of asthma lead to chronic airway inflammation, bronchoconstriction, and airway hyper responsiveness.

General overview of the pathophysiology of asthma:

Airway inflammation: Asthma's key feature is the inflammation of airways due to the abnormal accumulation of T-lymphocytes, neutrophils, and eosinophils, resulting in edema, heightened mucus production, and damage to epithelial cells.

***Bronchoconstriction*:** Bronchoconstriction is the constriction of the airways that occurs when the smooth muscles surrounding them contract. Inflammatory mediators, including histamine, leukotrienes, and prostaglandins, trigger this response by causing the smooth muscles to contract.

Airway hyperresponsiveness: Airway hyperresponsiveness occurs when the airways overreact to different stimuli like allergens, irritants, and physical activity. This is due to the increased airway smooth muscle sensitivity and the inflammatory cells' hyperresponsiveness.

Airway remodeling

When inflammation and bronchoconstriction persist, they can cause structural alterations in the airways, which results in goblet cell accumulation, smooth muscle mass expansion, and basement membrane hypertrophy. These modifications can result in long-term decline in pulmonary function and respiratory passage obstruction. (10,11,12) The airway remodeling results in asthma manifestations that predominantly include breathing difficulty, chest discomfort, cough, and wheezing.

Airway inflammation in asthma

Asthma-related airway inflammation develops due to the aggregation of macrophages, T lymphocytes, Mast cells, and eosinophils. In addition, the hyperactivation of growth factors, chemokines, cytokines and mediators of inflammation also trigger asthma in predisposed

Vol. 20, No. 1. (2024)
E ISSN: 1672-2531

individuals. In the development of asthma, inflammatory mediators trigger the inflammatory response in the respiratory passages. The structural, epithelial, and immune cells of the airways actively induce these inflammatory mediators. They work by attracting inflammatory cells to the site of inflammation, encouraging their activation and viability, and stimulating airway remodeling**.** Among the inflammatory mediators involved in asthma, cytokines are of particular importance. Cytokines are small soluble proteins that act as messengers between cells, regulating immune and inflammatory responses. Cytokines in asthma are produced by macrophages, mast cells, eosinophils, T lymphocytes, and other airway cells. Asthma pathogenesis progresses with IL-13/IL-4 activity leading to eosinophilic infiltration, airway inflammation, mucus production, and airway hyperresponsiveness; IL-4 is mainly generated by mast cells and Th2 lymphocytes. The expression of multiple genes related to inflammation and remodeling is the outcome of the IL-13/IL-4 activity on epithelial cells, fibroblasts, and smooth muscle cells of the respiratory passages. (13)

The effector cell/eosinophil survival and activation in asthma depends on IL-5 pathogenesis; IL-5 is generated by Th2 lymphocytes, epithelial cells, eosinophils, and mast cells. The cytokine binds to the eosinophil receptor and induces their activation and survival, ultimately leading to their recruitment to the airway. TNF-alpha is a cytokine that promotes inflammation which is linked to the development of asthma and is generated via epithelial cells, T-lymphocytes and macrophages. TNF-alpha interacts with a range of airway receptors, leading to the activation of genes that cause inflammation, apoptosis, and remodeling. (14,15)

Interleukin-1

The cytokine group IL-1 triggers inflammation and is vital to the body's natural defense mechanisms. These cytokines are generated after tissue injury, infection, or stress via epithelial/dendritic cells and macrophages. The mechanism of action of IL-1 involves attaching to its receptor on diverse cells, leading to the activation of genes that regulate inflammation, immunity, and the repair of tissues. IL-1 consists of two variants: IL-1α and IL-1β. Despite being structurally similar and having separate genes, they differ in their function and secretion methods. Macrophages and epithelial cells produce IL-1α, which is active even in its precursor form, anchored to the membrane, and released upon cellular damage or death. Activated macrophages mainly produce IL-1β, which is active only in its mature form, released through the process of active inflammation (16)

Evidence indicates IL-1 attribution to the development of numerous disease conditions, including inflammatory bowel disease, psoriasis, gout, osteoarthritis, and rheumatoid arthritis. Research shows that blocking IL-1 activity can be a successful strategy in treating specific diseases like rheumatoid arthritis and systemic juvenile idiopathic arthritis. Findings from various studies reveal the role of IL-1 in causing schizophrenia, depression, Alzheimer’s disease, and other neuropsychiatric conditions. Research indicates that IL-1 stimulates microglia and astrocytes, leading to neuroinflammation and neuronal damage. Preclinical studies also suggest that blocking IL-1 activity could enhance executive function in depression and Alzheimer’s disease. (17) IL-1's involvement in cancer pathogenesis has also been identified. Research demonstrates that IL-1 fosters tumor development and angiogenesis while it suppresses tumor cell apoptosis. However, studies have also shown that obstructing IL-1 activity in animal models of cancer can suppress tumor growth and metastasis. (18,19)

Interleukin-1 signaling in the lungs

The immune response of the lung and its inflammatory regulation depends up on the involvement of IL-1. Research indicates IL-1R1 utilization by IL-1β and IL-1α subtypes; their signaling pathways are intricate and involves various intracellular signaling pathways, which manage the transcription of genes, which are vital in the regulation of inflammation, immunity, and tissue repair. (20,21)

IL-1 is produced by epithelial cells, dendritic cells, and macrophages following inflammatory stimuli, infections, and allergen exposure. While epithelial cells are the primary source of IL-1α, it is biologically active in its precursor form, which is membrane-bound and can be released upon cell damage or necrosis. On the other hand, activated macrophages are the primary source of IL-1β, and it is only biologically active in its mature form, released during inflammatiory activation. (22,23) IL-1 signaling in the lungs governs the pathophysiology of several respiratory diseases, not limited to acute lung injury, COPD, and asthma. It triggers the expression of VCAM/ICAM-1, VCAM-1, TNF-α, IL-6, and other chemokines/proinflammatory cytokines. Lung inflammation and tissue damage are subsequently induced by the accumulation of T-cells, macrophages, and neutrophils. (24) The interleukin-1 receptor (IL-1R) on pulmonary epithelial/immune cells actively interacts with IL-1β/ IL-1α. Subsequently, the induction of IL-1R leads to the activation of intracellular signaling pathways including NF-κB, MAPKs, and JNK, which consequently triggers the production of adhesion molecules, chemokines, and pro-inflammatory cytokines. (25)

After infection, neutrophil deployment is effectively induced by IL-1β/1α. Neutrophils trigger the initial response against invading pathogens and are essential for controlling infections; CXCL1 and CXCL2 production is activated by IL-1β/ IL-1α, and they are responsible for attracting neutrophils to the site of infection. (26) Dendric cells are activated by IL-1β/IL-1α and are responsible for T-cell-antigen interactions. They effectively add to the adaptive/cell-mediated immunity in various disease conditions. The dendritic cell activation improves the accumulation/differentiation of IFN-γ and Th1 cells. (27,28) The severity of asthma is indicated by IL-1β/1α elevation, which is confirmed by bronchoalveolar lavage. The preclinical studies indicate airway remodeling and hyperresponsiveness, triggered by IL-1 in asthmatic conditions.

COPD is induced by IL-1 and progresses with emphysema, bronchitis, and chronic inflammation. IL-1 has been suggested to play a key role in the development of COPD. The bronchoalveolar lavage reveals IL-1β/ IL-1α elevation in patients with asthma. Moreover, IL-1 has been shown to upregulate the expression of matrix metalloproteinases (MMPs), which leads to the gradual deterioration of pulmonary tissues. (18) Acute lung injury is a respiratory illness that causes inflammation and tissue harm in the lungs and is triggered by IL-1 accumulation. Patients with acute lung injury have IL-1β/ IL-1α elevations, which are known to trigger neutrophils and inflammatory cytokines. (28)

Asthma pathogenesis and the role of IL-1

Asthma's pathogenesis correlates with the combined activity of the adaptive and innate immune systems. Asthma advances with IL-1 hyperactivity leading to the immune response. IL-1 can activate dendritic cells, which induce T cell-antigen interactions. This stimulation leads to the T cell activation/differentiation into Th2 cells, which are responsible for activating IL-13/4/5 cytokines, which have a pivotal role in the pathogenesis of asthma (29). IL-1 effectively induces Th2/dendritic cells and triggers the accumulation of IL-13/5/4. It also produces Th2 cells from the

naive T-cells. It also activates eosinophils and their recruitment in airways adds to the pathogenesis of asthma.

MAPK and NF-κB signaling pathways are activated by IL-1β and IL-1α, which results in the accumulation of CCL2, CCL3, CCL5, IL-6, TNF-α, and other proinflammatory cytokines in the respiratory passages; the NLRP3 inflammasomes are activated by IL-1β and IL-1α, which eventually leads to further aggregation of neutrophils and IL-1β in the respiratory passages. (30,31)

IL-1β is capable of inducing hyperresponsiveness in the respiratory passages, which is a crucial attribute of asthma. This molecule does so by promoting mucus accumulation and smooth muscle contraction in the airways. IL-1β can also promote the development of airway remodeling, a long-term consequence of asthma, by inducing the production of extracellular matrix proteins and fibroblast proliferation. (32)

The activation of airway epithelial cell is initiated by IL-1β/ IL-1α, which are essential contributors to the development of asthma. VCAM-1 and ICAM-1 adhesion molecules are induced by IL-1, leading to immune cell recruitment in patients with asthma. Additionally, IL-1 is capable of inducing the synthesis of mucins, resulting in excessive mucus accumulation in asthma. IL-1 can also promote the production of IL-8, thereby triggering inflammatory reactions. (34 - 36) IL-1β/1α, play a pivotal part in the development of asthma. This molecule activates immune cells, promotes inflammation, induces AHR, and contributes to airway remodeling. Additionally, IL-1 plays a crucial role in activating airway epithelium in asthma. Hence, targeting IL-1 and its signaling pathways might be a valuable therapeutic approach for managing asthma.

Asthma pathogenesis mitigation by IL-1 targeting IL-I

Due to its role in asthma pathogenesis, IL-1 targeting has become a promising therapeutic strategy for managing asthma. Various agents aimed at IL-1 and its signaling pathways have undergone clinical trials.

Anakinra curtails the pro-inflammatory effects of IL-1β/IL-1α by restricting their interactions with the corresponding receptors; however, its therapeutic efficacy against asthma is inconsistent in few clinical studies. (37,38) An RCT has recently revealed lung function improvement and a decline in airway responsiveness in patients treated with anakinra for asthma. (39) Alternatively, another study revealed opposite outcomes negating the lung function improvement role of anakinra in patients with asthma. (40) The efficacy of the IL-1β targeting monoclonal antibody benralizumab against asthma is widely debated in the medical literature. Findings from a Randomized Control Trial (RCT) revealed a minimization of asthma exacerbations in 89 asthma subjects, who were treated with anakinra. Contrarily, another RCT failed to demonstrate the therapeutic efficacy of anakinra in 653 asthma subjects receiving anakinra treatment. (41) Findings from another RCT indicated minimization in airway hyperresponsiveness and lung function improvement in 52 patients receiving mavrilimumab for severe and uncontrolled asthma management. (42)

A recent study shows an improvement in lung function and a reduction in airway hyperresponsiveness in 240 asthma subjects, who were treated with gevokizumab. Another study following a similar design failed to demonstrate the therapeutic advantage of gevokizumab in 300 subjects with asthma complications. (43) Clinical trials targeting the IL-1 pathway for asthma treatment have produced varied results, with some demonstrating significant improvements in asthma control and lung function while others did not. The cause of these inconsistencies is not entirely clear, but it may be due to differences in patient characteristics, dosing schedules, or the specific agent used. Nevertheless, targeting the IL-1 pathway remains an attractive therapeutic approach for asthma treatment since IL-1 is involved in various aspects concerning the

pathogenesis, like inflammation, hyperresponsiveness, and airway remodeling. Targeting IL-1 has the potential to be effective for patients who do not respond to conventional therapies. Identifying optimal agents and dosing schedules for targeting the IL-1 pathway and developing biomarkers that predict response to IL-1-targeted treatments is important for future research. In conclusion, despite the mixed results, the broad-spectrum effects of targeting IL-1 make it a promising avenue for the development of new therapies for asthma.

Tumor Necrosis Factor-Alpha

The pro-inflammatory cytokine (TNF-alpha) regulates inflammation and cell survival in the immune system. It is mainly synthesized by immune cells and macrophages. The activation of immune cells is followed by infection, injury, or stress. The eventual accumulation of natural killer cells, T cells, and B cells triggers asthma exacerbation; TNF-α belongs to a class of cytokines, which encompasses lymphotoxin-α, lymphotoxin-β, TNF-β, and other related proteins. TNF-α participates in numerous physiological and pathological processes, including cell migration, differentiation, apoptosis, and proliferation. As far as the immune system is concerned, it acts as a crucial mediator of inflammation and has an important function in preventing infections. It favors immune cell induction at the injury or infection site. The high accumulation of lymphocytes, neutrophils, and macrophages eventually adds to the pathophysiology of asthma exacerbation. (44) The abnormal TNF-α accumulation leads to the induction of a range of chronic conditions including asthma, psoriasis, rheumatoid arthritis, and Crohn's disease. The high expression of TNF-α also results in persistent inflammation and tissue damage. (45)

Activated T cells, eosinophils, and macrophages in the airways produce TNF-α in asthma, leading to airway inflammation. This proinflammatory cytokine boosts eosinophil activation and migration and induces IL-13/IL-5 and similar cytokines. In addition, TNF-α induces muscle contraction and mucus production, leading to airway hyperresponsiveness. (46) The involvement of TNF-α in the development of asthma has been better understood through clinical trials assessing the effectiveness of anti-TNF-α therapies, including etanercept and infliximab. These medications demonstrated the ability to decrease airway inflammation, enhance lung function, and reduce the reliance on rescue medications in severe asthma patients. Despite these benefits, the response to anti-TNF-α therapy can vary, and some patients may not benefit from this treatment.

TNF- α Biology and signaling

TNF-α is a crucial cytokine with diverse effects that regulate immune system homeostasis. Its production is primarily triggered by inflammatory stimuli, microbial products, or cytokines and is mainly synthesized by the induction of T cells, natural killer cells, and macrophages. The signaling of TNF-α involves two receptors present on the cell membrane, TNFR1 and TNFR2, which trigger distinct downstream signaling pathways and induce different biological responses. (47)

TNFR1 is expressed by most cell types and triggers apoptosis and NF-$_K$-beta mechanism. Upon TNF-α binding, the receptor recruits the adapter protein TRADD, which activates other proteins like FADD and caspase-8, initiating the apoptotic cascade. TNFR1 activation also induces the IKK complex, which phosphorylates IκBα, promoting its ubiquitination and deterioration of the proteasome. These processes facilitate inflammation, cell survival, and immune upregulation by activating the cellular function of NF-κB. (48-50)

TNFR2 is mainly present in immune cells, neurons, and endothelial cells, and triggers the non-canonical NF-κB pathway, leading to NIK activation and p52 transformation from p100. Additionally, TNFR2 activation induces cell survival and proliferation by activating the AKT and MAPK signaling pathways. Recent evidence demonstrates the role of the signaling of NF-κB in

the induction of multiple sclerosis, inflammatory bowel disease, psoriasis, and rheumatoid arthritis. In these conditions, the overproduction of TNF-α leads to chronic inflammation, immune dysfunction, and tissue damage. Hence, the modulation of TNF-α signaling for therapeutic purposes might be the subject of extensive research.

Various anti-TNF-α treatments have been developed to manage autoimmune/inflammatory conditions, including psoriasis, Crohn's disease, and rheumatoid arthritis. These modalities incorporate etanercept/TNF receptors, adalimumab/infliximab, and other monoclonal antibodies. They have demonstrated efficacy in alleviating inflammation and improving disease outcomes in many patients. (51-53) However, the use of anti-TNF-α therapies is not without potential drawbacks. Patients may experience lymphoma, latent tuberculosis recurrence, and relapse of other similar infections. Additionally, some patients may not respond to these treatments or may develop resistance to them over time.

Role of TNF- α in the asthma paradigm

Airway epithelial cells respond to TNF-α by producing chemokines and adhesion molecules that attract and activate immune cells, ultimately leading to the development of inflammation. Moreover, TNF-α induces airway hyperresponsiveness (AHR) by inducing airway narrowing and bronchoconstriction via smooth muscle cell activation in the respiratory passages (54). Direct modulation of airway smooth muscle cells is another process used by TNF-α which contributes to trigger the pathogenesis of asthma. By inducing the production of ROS in these cells, TNF-α activates the RhoA/ROCK pathway, which in turn leads to increased airway contraction and AHR. Additionally, TNF-α can result in fibrosis/airway remodeling by the activation of smooth muscle cells and extracellular matrix proteins. (55-59) Associations have been observed between asthma susceptibility and TNF-α SNPs. These SNPs can impact TNF-α expression and function, thereby influencing immune responses and promoting inflammation in the airways

Another significant pathway by which TNF-α contributes to the development of asthma is through TNF-α-induced oxidative stress. This occurs when TNF-α induces RNS/ROS in the immune cells and the airway epithelium. This can cause damage to tissues through oxidative stress, resulting in the induction of signaling processes engaged in inflammation/airway remodeling, which can lead to asthma progression. TNF-α signaling modulation research has been actively pursued to find novel therapies for asthma. The effectiveness of anti-TNF-α therapies like infliximab and etanercept in reducing inflammation and enhancing pulmonary function in uncontrolled asthma has been established. However, their application is restricted due to potential adverse efffects including malignancies and infections. Therefore, developing more precise therapies that can selectively modulate TNF-α signaling in specific cell types or pathways is necessary to improve asthma outcomes. (59-61)

Clinical trials investigating Anti-Tumor Necrosis Factor-Alpha in asthma management.

The significance of TNF-α in asthma induction has been well-established, and there is growing interest in targeting TNF-α for asthma management. Several clinical trials in this regard have produced conflicting outcomes. This paper reviews recent studies investigating asthma management with TNF-α.

Golimumab

A recent RCT in Japan evaluated the clinical outcomes of a human monoclonal antibody (subcutaneous golimumab) based on its TNF-α inhibition potential in asthma. The outcomes substantiate the role of this entity in improving asthma control by minimizing respiratory

exacerbations and improving pulmonary function. The adverse events included URTIs and injection site reactions. (62)

Infliximab

An RCT in Korea indicates the asthma management potential of IV infliximab based on its TNF-α inhibition activity in uncontrolled asthma. The outcomes shows marked improvement in lung function and in control of asthma. However, patients experienced a high incidence of URTI and its respiratory complications. (28)

Etanercept

An RCT conducted in the United States examined the effectiveness and safety of subcutaneous etanercept, a soluble TNF-α receptor that inhibits TNF-α activity in asthma; results showed that etanercept did not significantly improve lung function and asthma exacerbation rates. In addition, patients had a high incidence of injection site reaction and URTI. (29)

Adalimumab

An RCT conducted in Europe investigated the effectiveness and safety of subcutaneous adalimumab based on its TNF-α inhibition ability in asthma. The outcomes indicated no improvement in asthma exacerbation/lung function; URTI was the most frequently reported adverse reaction. (30)

Certolizumab

An RCT conducted in the United States assessed certolizumab for its clinical outcomes based on its TNF-α inhibition capacity, in patients with uncontrolled asthma. The outcomes negated its role in improving lung function/asthma control. The most reported adverse events were injection site reactions and upper respiratory tract infections. (31)

Asthma management with TNF-α inhibition treatments is debatable and requires further investigation by RCTs with larger sample sizes. While certain studies have reported significant enhancements in asthma control and lung function with anti-TNF-α agents, others have failed to show a significant benefit. Adverse effects linked to anti-TNF-α therapy have generally been mild and controllable, however, additional investigation is required to assess their safety and long-term implications.

CONCLUSION.

Asthma-related airway inflammation is a complex process involving IL-1, TNF-α, and other mediators of inflammation. These cytokines are crucial in promoting airway inflammation, eosinophilic infiltration, mucus production, and airway hyperresponsiveness in asthma. Therefore, comprehending the role of these cytokines in asthma pathogenesis could provide new avenues for asthma treatment. However, more research should investigate their precise function in asthma and the effectiveness of anti-TNF-α and IL-1 therapies.

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Author Contribution:

Dr. Santhosh Kumar S.V conceptualized the study, designed the research methodology, collected and analyzed the data, and wrote the manuscript.
Dr. Mohan C.K and **Dr. Sisir P.R** supervised the research, provided critical feedback, and revised the manuscript for important intellectual content.
Dr. Abina Augustine contributed to data collection, analysis, and interpretation, and assisted in drafting the manuscript.
Dr. Sivaramyapragathi R.S contributed to data collection, literature review, and manuscript preparation.
All authors reviewed and approved the final version of the manuscript.