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Case Report

The Role of Nf-kB and Nrf2 Transcription Factors Inhibitors in Bronchial Asthma: A Case Report

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Abstract

Bronchial asthma is a chronic respiratory condition characterized by airway inflammation and bronchial hyperreactivity, influenced by genetic, environmental, and immunological factors. The pathogenesis involves chronic inflammation mediated by immune cells and pro-inflammatory cytokines, with critical roles played by the transcription factors Nf-kB and Nrf2. Omaveloxolone, an investigational drug for Friedreich's Ataxia, modulates the Nrf2 pathway and inhibits Nf-kB, potentially offering therapeutic benefits in asthma management. Preliminary studies suggest that Nrf2 activation may improve lung function and reduce inflammation in asthmatic patients, warranting further research to explore its efficacy and safety in this context.

Keywords: Asthma; Pulmonology; NF-Kb; Nrf2; Trascription Factors; Ataxia; Inhibitors

Introduction

Bronchial asthma is a chronic respiratory disease affecting millions of people worldwide, characterized by airway inflammation, bronchial hyperreactivity, and variable airflow obstruction. According to the latest GINA guidelines for 2024-2025, asthma results from a complex interplay of genetic, environmental, and immunological factors [1]. The pathogenesis of asthma is primarily mediated by chronic inflammation involving various immune cells, including eosinophils, mast cells, and T lymphocytes, which release a variety of cytokines and chemical mediators. Chronic inflammation in asthma is characterized by excessive activation of the immune system, leading to increased production of pro-inflammatory cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) [2]. These cytokines not only promote the infiltration of eosinophils and mast cells into the airways but are also responsible for mucus production and hyperplasia of smooth muscle cells, thereby

contributing to bronchial obstruction and respiratory difficulty [3]. A crucial aspect of the pathogenesis of asthma is represented by intracellular signaling pathways, particularly those mediated by the transcription factors Nf-kB and Nrf2. Nf-kB is a transcription factor that, once activated by inflammatory stimuli such as cytokines and allergens, translocates to the cell nucleus and promotes the expression of genes involved in the inflammatory response. This leads to an increase in the production of pro-inflammatory cytokines and perpetuates the inflammatory process, contributing to bronchial hyperreactivity and exacerbation of asthmatic symptoms [4]. On the other hand, Nrf2 is a transcription factor that plays a fundamental role in the antioxidant response and cellular protection. Under normal conditions, Nrf2 is maintained in an inactive state in the cytoplasm, but in response to oxidative stress and inflammation, it dissociates from inhibitory proteins and translocates to the nucleus, where it activates genes encoding for antioxidant enzymes and cellular defense proteins. Adequate activation of Nrf2 is essential to counteract the inflammation and tissue damage associated with asthma. The balance between the Nf-kB and Nrf2 signaling pathways is crucial for managing chronic inflammation in asthma [5]. Dysregulation of this balance can lead to exacerbation of symptoms and disease progression. This case report focuses on a young patient with bronchial asthma, obstructive sleep apnea syndrome, and Friedreich's ataxia, highlighting the clinical challenges and therapeutic implications associated with this complex conditions.

Case Report

A 47-year-old young woman affected by Friedreich's Ataxia since birth came to the private clinic "La Madonnina" for reported respiratory symptoms including shortness of breath, wheezing, dry cough, nighttime awakenings, and sleep apnea. She was clinically evaluated, and a full spirometry test was performed, showing a positive bronchodilator response for asthma. Nighttime cardiorespiratory monitoring was also carried out, revealing severe obstructive sleep apnea syndrome with latent nocturnal respiratory failure. Consequently, a maximal asthma therapy and nighttime CPAP therapy were initiated, resulting in a reduction of asthma exacerbations throughout the year. However, since January 2025, she started Omaveloxolone, a medication for ataxia, under neurological specialist guidance, and returned to my attention in September 2025 after 9 months of experimental therapy. He underwent the first comprehensive spirometry with a bronchodilator reversibility test; and follow-up spirometries during therapy with ICS/LABA/LAMA and Omaveloxolone, using the PulmOne MiniBox + Spirometer, and the results are very interesting, as they showed an improvement in lung volumes with a reduction in the Motley index and residual volume at 9 months with new target therapy. It seems that this drug may have therapeutic potential not only for Friedreich's Ataxia but also for bronchial asthma and other respiratory diseases. the patient underwent approximately 9 months of therapy with ICS/LABA/LAMA and omaveloxolone, an inhibitor of NF-κB and Nrf2, showing significant improvement in all lung volumes as well as an increase in inspiratory capacity and lung desufflation. In fact, the residual volume was significantly reduced and motley index(RV/TLC) was significantly reduced; with an improves of inspiratory capacity (See Table 1). Proinflammatory proteins overexpressed in the context of the inflammatory process that characterizes asthma, such as cytokines, chemokines, adhesion molecules, enzymes, and receptors responsible for the synthesis and biological effects of various mediators, are encoded by genes regulated by different transcriptional factors. These factors therefore act as nuclear messengers, as they have the property of converting short-lived stimuli from the extracellular environment into relatively prolonged modifications of gene transcription. NF-kB stimulates the transcription of numerous inducible genes encoding proteins of significant importance in the inflammatory process characterizing asthma, such as proinflammatory cytokines and growth factors, chemokines, and adhesion molecules involved in the recruitment of inflammatory cells, as well as enzymes responsible for the synthesis of various mediators. From what emerges from the case report, it would appear that omaveloxolone blocks these signaling pathways and inhibits the formation of pro-inflammatory molecules in asthma as well as acting on ataxia.

Discussion

Omaveloxolone is an investigational drug that has shown promising results in the treatment of Friedreich's Ataxia (FRDA), a hereditary neurodegenerative disease characterized by the degeneration of neurons and loss of motor coordination. The pathogenesis of FRDA is primarily associated with a deficiency of frataxin, a mitochondrial protein involved in iron regulation

Spirometric parameters calculated	Predicted Value (pre BD)	Predicted Value(postBD)	Percentage change from predicted value	Predicted Value 9 months with ICS/ LABA/LAMA + Omaveloxolone
FEV1	1,71L -55%	1,97L - 63%	+8%	2,66L - 88%
FVC	2,42L - 63%	2,68L - 69%	+6%	3,17L - 84%
FEV1/FVC	70.68%	73.67%	+3%	85.26%
FEF 25-75	1,21L/sec - 39%	1,54L/sec - 49%	+10%	3,13L/sec - 105%
PEF	2,61L/sec - 38%	3,54L/sec - 52%	+14%	4,12L/sec - 61%
TLC	4,34L - 77%	/	/	4,48L - 80%
RV	1,92L - 129%	/	/	1,31L - 84%
RV/TLC	44,29- 168%	/	/	29,22- 106%
IC	1,88L - 68%	/	/	2,22L - 81%

Table 1: Global Spirometry with PulmOne MiniBox+. Global Spirometric values indicating the presence of significant variation in PEF after use of ICS/LABA/LAMA for one months in absolute value (+930ml post bronchodilation + 14%). The diagnosis of bronchial asthma is confirmed based on significant changes in PEF. As can be seen from the table, the patient underwent approximately 9 months of therapy with ICS/LABA/LAMA and omaveloxolone, an inhibitor of NF-κB and Nrf2, showing significant improvement in all lung volumes as well as an increase in inspiratory capacity and lung desufflation. In fact, the residual volume was significantly reduced (-45% predicted, equal to -610 ml).

Legend: FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; FEV1/FVC, Forced Expiratory Volume in 1 second to Forced Vital Capacity ratio; FEF 25-75, Forced Expiratory Flow 25-75%; PEF, Peak Expiratory Flow; TLC, Total Lung Capacity; RV, Residual Volume; RV/TLC, Residual Volume to Total Lung Capacity ratio; IC, Inspiratory Capacity; BD, Bronchodilator.

and protection against oxidative stress [6]. The lack of frataxin leads to iron accumulation in the mitochondria, causing cellular damage and neuronal death. Omaveloxolone acts as a modulator of the Nrf2 (Nuclear factor erythroid 2-related factor 2) signaling pathway, a crucial transcription factor for the antioxidant response and cellular protection. In FRDA, the activation of the Nrf2 pathway is compromised due to oxidative stress and chronic inflammation. Omaveloxolone stimulates the activation of Nrf2, promoting the translocation of this transcription factor into the nucleus, where it induces the expression of antioxidant and cellular protective genes. In particular, Omaveloxolone inhibits the NF-kB signaling pathway, another transcription factor that regulates inflammation and the immune response. The activation of NF-kB is associated with inflammatory and neurodegenerative processes, and its inhibition by Omaveloxolone helps reduce inflammation and oxidative stress in the central nervous system. This dual mechanism of action—activation of Nrf2 and inhibition of NF-kB—provides an innovative therapeutic approach to address the complex molecular alterations associated with FRDA [7,8]. Clinical studies have demonstrated that Omaveloxolone can improve neurological function and quality of life in patients with Friedreich's Ataxia, suggesting that modulation of redox and inflammatory signaling pathways may have a significant impact on disease progression. However, it is essential to continue monitoring the long-term effects and safety of the drug in larger populations to confirm its efficacy and tolerability profile. Additionally, emerging evidence suggests a potential role for Omaveloxolone in asthma. Asthma is characterized by chronic inflammation of the airways, and modulation of the Nrf2 pathway may contribute to enhancing the antioxidant response and reducing inflammation [9]. Some studies have indicated that Nrf2 activation may have beneficial effects in the context of asthma, improving lung function and reducing bronchial hyperreactivity [10]. It is interesting to note how the drug for Friedreich's ataxia may have positive effects in different contexts, such as bronchial asthma. The reduction of inflammation and static lung volumes, such as residual volume and the Motley index, suggests that there may be potential to develop new targeted therapies to improve asthma management, paving the way for further research in this

area. However, research on Omaveloxolone specifically for asthma is still limited and requires further investigation to establish its efficacy and safety in this context.

Conclusion

The interplay between chronic inflammation and oxidative stress in asthma underscores the importance of targeted therapeutic strategies. Omaveloxolone's dual mechanism of action—activating the Nrf2 pathway while inhibiting Nf-kB—presents a promising avenue for addressing the underlying pathophysiology of asthma. While initial findings are encouraging, comprehensive clinical trials are essential to validate the safety and efficacy of Omaveloxolone in asthma treatment. Future research should focus on elucidating the potential benefits of Nrf2 modulation in enhancing antioxidant defenses and reducing airway inflammation, ultimately improving patient outcomes in bronchial asthma.

Authors' Contributions

FF and MUS helped in the conception and design of the study; MUS did data collection, analysis, and interpretation of data; MUS, FF and CP contributed to drafting the work and revising it critically for important intellectual content; GS translated the paper to English. All authors approved the final version for publication and agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare no potential conflict of interest.

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Ethics Approval and Consent to Participate

Informed consent was signed by the patient.

All mentioned ethical aspects and related consents were taken into consideration during the conduct of this study.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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