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Renoprotective efficacy of montelukast; an overview on recent advancements

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ABSTRACT

Montelukast holds significant promise as a renoprotective agent, especially in early-stage kidney injuries. Its multifaceted mechanisms—ranging from anti-inflammatory and antioxidant actions to neutrophil inhibition—underscore its potential utility in clinical settings. Montelukast should not be used in patients with a known hypersensitivity to the drug or its components. Caution is advised for individuals with a history of psychiatric disorders or those who have phenylketonuria (PKU), as some formulations contain phenylalanine.

Keywords: Montelukast, Acute kidney injury, Chronic kidney disease, Antioxidant

Mini-Review

Implication for health policy/practice/research/medical education:
Montelukast as a leukotriene receptor antagonist, with several protective effects against kidney damage caused by chemotherapy. Montelukast reduces inflammation in renal tissues, which is crucial during chemotherapy-induced nephrotoxicity.

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Introduction

Montelukast is a leukotriene receptor antagonist primarily used in the management of asthma and allergic conditions. Montelukast works by selectively blocking the action of leukotriene D4 (LTD4) at the cysteinyl leukotriene receptor type 1 (CysLT1) (1). This inhibition reduces inflammation, bronchoconstriction, and mucus secretion associated with asthma and allergic reactions (2,3). The drug demonstrates significant efficacy in reducing asthma symptoms and improving lung function, particularly when used alongside inhaled corticosteroids (2,3). This agent is approved by the FDA in 1998 too (4). Recent studies indicate that montelukast may have renoprotective properties, particularly in the context of acute kidney injury and other renal dysfunctions (5). Following inhibition of cysteinyl leukotrienes, it mitigates inflammatory responses that can exacerbate kidney injury (6). This compound also enhances the balance between oxidants and antioxidants, reducing oxidative damage to kidney cells. This efficiency is particularly important given that many chemotherapeutic agents induce oxidative stress (6,7). Further, this compound decreases neutrophil infiltration in the kidneys, which is often a contributor to tissue damage during inflammatory responses associated with chemotherapy (8). Numerous studies have demonstrated montelukast protective effects in animal models of nephrotoxicity (9). For instance, it has shown montelukast efficacy in preventing kidney damage induced by chemotherapeutic agents, where montelukast treatment led to the improved renal function markers and reduction of histopathological damage (10). Meanwhile, in human studies, montelukast has been evaluated for its role in managing renal complications associated with chemotherapy (9,10). On the other hand, several reports indicate positive outcomes in terms of improved kidney function and reduced incidence of nephrotoxicity among patients receiving chemotherapy (10,11). Recent studies, had shown that, montelukast has been particularly noted for its protective effects against drugs like cisplatin and methotrexate, both of which are known to cause significant renal impairment (10,12). Accordingly, in the models of rhabdomyolysis-induced acute renal failure, montelukast improved glomerular filtration rate and reduced markers of kidney injury. It modulates cytokine production and enhances antioxidant capacity, thereby reducing the severity of kidney injury associated with muscle breakdown (13). Additionally, there are reports concerning positive outcomes for montelukast in treating

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conditions like nephrotic syndrome and pyelonephritis (14,15). In pediatric patients with pyelonephritis, montelukast led to rapid clinical improvement (14,16). Notably, administration of this drug, has been associated with reduced corticosteroid requirements and improved clinical manifestations in pediatric patients suffering from renal disease (17). Likewise, montelukast has demonstrated protective effects in ischemia-reperfusion models, which are critical in understanding kidney injuries related to surgical procedures or trauma. This agent preserved renal structure and function by reducing oxidative stress and inflammation during reperfusion (18). Furthermore, in cases of nephrotoxicity due to drugs like diclofenac and cyclosporine, montelukast has been effective in minimizing renal damage (19,20). Previous studies shown, initiating montelukast shortly after chemotherapy exposure can still provide benefits, though this capability may be less pronounced than with pretreatment (21,22). Studies have shown that administering montelukast within a few days post-exposure can help ameliorate renal biomarkers, but the outcomes are often not as robust as those seen with pretreatment strategies. In clinical practice, this timing consideration underscores the importance of early intervention when patients are at risk for chemotherapy-induced nephrotoxicity (23). Oncologists may consider integrating montelukast into preemptive strategies for patients receiving high-risk chemotherapeutic agents (24). This short-review sought to study the most recent concepts on kidney protective efficacy of montelukast and its possible renoprotective impact in chronic kidney disease (CKD).

Search Method

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords like; Montelukast, acute kidney injury, chronic kidney disease and antioxidant efficacy.

Administration of montelukast for kidney protection

Recent investigation indicated that montelukast can lower serum creatinine and urea levels, indicating improved kidney function (16). These studies also demonstrated that pretreatment with montelukast is often more effective than treatment when kidney injury has occurred (13). This efficacy suggests that early intervention is crucial for maximizing its protective effects (25). Age-related physiological changes can affect drug metabolism and response (26). Additionally, gender differences in drug pharmacodynamics may also play a role in how effectively montelukast works in different populations (27). Prolonged administration of montelukast has been associated with greater efficacy in reducing kidney damage (28). Continuous administration allows for sustained drug levels in the bloodstream, enhancing its protective effects against renal injury (16,28). In experimental models, longer durations of montelukast administration resulted in better preservation of kidney function and reduced markers of oxidative stress (28,29). Montelukast has been shown to decrease levels of malondialdehyde (MDA), a marker of lipid peroxidation, indicating reduced oxidative damage in renal tissues (16,26). This effect is particularly evident in models of nephrotoxicity, where montelukast administration leads to lower oxidative stress indices and enhanced antioxidant capacity (29). Unlike some antioxidants that may deplete tissue stores of glutathione (GSH), montelukast appears to support and maintain these stores. Studies indicate that its antioxidant effect does not significantly consume GSH, allowing for sustained antioxidant defenses within the kidney (10,16). Montelukast has been associated with increased activity of key antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPX) (31,32). These enzymes play vital roles in detoxifying reactive oxygen species (ROS) and protecting cellular structures from oxidative damage (31,32). As mentioned, following inhibiting neutrophil infiltration, montelukast reduces the inflammatory response and prevents further oxidative damage to renal tissues, which enhancing overall kidney protection (16, 28). Montelukast has been shown to lower the levels of pro-inflammatory cytokines and mediators such as tumor necrosis factor-alpha (TNF-α) and monocyte chemoattractant protein-1 (MCP-1) (33). These mediators are crucial for neutrophil recruitment to inflamed tissues. By reducing their production, montelukast decreases the inflammatory response, leading to less neutrophil infiltration in renal tissues (34,35). Some studies suggest that montelukast may also influence the apoptosis of neutrophils, promoting their resolution from inflamed tissues (36). By modulating apoptotic pathways, montelukast can help clear activated neutrophils from the kidneys more effectively, thereby reducing ongoing inflammation and tissue damage (36,37).

Ameliorative impact of montelukast on chronic kidney disease

Montelukast shows capability as a therapeutic agent for CKD due to its ability to reduce inflammation and oxidative stress (28). Current studies support its use in early-stage kidney injuries (16). The gradual progression of CKD often involves complex pathophysiological changes that may not respond as readily to montelukast alone (16,38). Additionally, a recent study involving a large cohort of veterans indicated that the use of leukotriene inhibitors like montelukast was linked to a significantly lower risk of developing end-stage kidney disease (ESKD) compared to non-users (39). Some studies suggest potential benefits in reducing proteinuria as well (40).

Conclusion

Montelukast exhibits a diverse ability to protect against various types of kidney injuries through multiple

mechanisms, including anti-inflammatory and antioxidant effects. Its effectiveness varies depending on the specific injury type, with notable benefits observed in AKI, nephrotoxic conditions, and ischemic injuries. Further research is needed to optimize its use across different renal pathologies and understand its long-term implications in chronic conditions.

Authors' contribution

Conceptualization: Sayed Yousef Mojtahedi, Sayed Yousef Mojtahedi.
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Investigation: Paniz Pourpashang.
Resources: Maryam Ghodsi.
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Visualization: Paniz Pourpashang.
Writing–original draft: Paniz Pourpashang.
Writing–review and editing: Sayed Yousef Mojtahedi, Maryam Ghodsi.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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