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Navigating Prednisone Contraindications: A Call For Alternative Solutions

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Abstract

Prednisone, a synthetic corticosteroid, is widely used for managing inflammatory and autoimmune disorders such as asthma, lupus, rheumatoid arthritis, and hypersensitivity pneumonitis. However, its efficacy is overshadowed by numerous contraindications and adverse effects, necessitating the exploration of safer alternatives. Prednisone is unsuitable for individuals with conditions like liver dysfunction, heart failure, diabetes, epilepsy, osteoporosis, and glaucoma. It is also contraindicated in cases of infections, including chickenpox, shingles, and measles, and possess risks of pregnant or breastfeeding individuals. Prolonged use often results in severe complications such as adrenal insufficiency, osteoporosis, and increased infection susceptibility. Emerging therapeutic approaches aim to overcome these limitations. Non-steroidal anti-inflammatory drugs (NSAIDs) offer localized anti-inflammatory effects with fewer systemic risks, while biologics and cytokine inhibitors provide targeted immune modulation. Natural compounds, including polysaccharides from *Hippophae rhamnoides* L. (sea buckthorn), curcumin and resveratrol, have demonstrated anti-inflammatory properties present viable alternatives for patients unable to tolerate prednisone. Lifestyle interventions, including anti-inflammatory diets, also hold promises for reducing dependency on pharmacological agents. This review highlights the pressing need to develop and prioritize substitutes for prednisone, especially for vulnerable populations with contraindications. Particular attention is given to sea buckthorn, which have shown significant potential in modulating immune responses and reducing oxidative stress. When used in combination with adjuvant therapies such as albuterol, cetirizine, epigallocatechin gallate, and pirfenidone, these natural compounds can target multiple pathways. Bridging gap in treatment options through multidisciplinary research is crucial to mitigate the risks of prednisone and improve the quality of care for individuals with inflammatory disorders. This article underscores the urgency of innovation in corticosteroid alternatives, advocating the enhanced safety, efficacy, and accessibility in the treatment of inflammation and immune-mediated conditions.

Keywords: Prednisone alternatives, Hypersensitivity pneumonitis, Sea buckthorn, Anti-inflammatory therapies, Pulmonary fibrosis prevention.

Introduction

For many years, prednisone, a synthetic glucocorticoid, has been a common component of treatment plans for autoimmune and inflammatory diseases. Because of its strong anti-inflammatory and immunosuppressive qualities, it is an essential treatment for a variety of chronic illnesses, including hypersensitivity pneumonitis, rheumatoid arthritis, systemic lupus erythematosus, and asthma.[1] Despite its demonstrated effectiveness, prednisone use is difficult, mostly because of its long list of side effects and contraindications. These modifications highlight how urgently safer, more efficient alternatives that can offer therapeutic benefits without endangering patient safety must be investigated and given priority. [2]

Hypersensitivity pneumonitis (HP), for example, is a condition characterized by inflammation of the alveoli in the lungs due to repeated exposure to environmental antigens, such as mold, bird droppings, or certain chemicals like isocyanates. Prednisone is often prescribed to manage the acute inflammatory response in hypersensitivity pneumonitis, providing rapid relief by suppressing the immune system.[3] However, long-term use of prednisone in such cases can lead to severe adverse effects, including osteoporosis, hyperglycemia, and increased susceptibility to infections, which can complicate disease management and reduce the patient's quality of life.[4] Approximately, 36.5% of patients do not respond to corticosteroids, particularly those with fibrotic HP.[5]

Prednisone works by mimicking cortisol, a natural hormone produced by the adrenal glands, which plays a critical role in regulating the immune response and inflammation. However, this mechanism also leads to widespread suppression of immune function, which is beneficial in autoimmune and inflammatory conditions but poses significant risks in patients with infections, impaired wound healing, or those who are immunocompromised.[6] Individuals, with pre-existing health conditions such as liver dysfunction, diabetes, hypertension, osteoporosis, and glaucoma are particularly vulnerable to the adverse effects of prednisone, which can exacerbate these conditions. Additionally, its use during pregnancy and breastfeeding is limited due to potential teratogenic effects and concerns about transmission to the infant through breast milk.[7]

The list of adverse effects associated with long-term prednisone use is extensive. Prolonged use can lead to osteoporosis, adrenal insufficiency, hyperglycemia, hypertension, Cushing's syndrome, and increased susceptibility to infections. These side effects often necessitate tapering or discontinuation of the drug, leaving patients in search of alternative treatments. For those with contraindications to corticosteroids, the therapeutic landscape becomes even more challenging, as there are limited options that match its efficacy without compromising safety.[8-11]

Given these limitations, there is a growing recognition of the need for alternative therapies that can offer comparable anti-inflammatory and immunosuppressive benefits without the associated risks. Over the past few years, significant progress has been made in developing and identifying alternative approaches to managing inflammation and autoimmune conditions. NSAIDs provide effective inflammation control with a more favourable safety profile for some patients, although they too have limitations, particularly in those with gastrointestinal or cardiovascular risks. Biological therapies, such as monoclonal antibodies and cytokine inhibitors, offer targeted immune modulation, reducing the risk of systemic side effects. However, these therapies are often expensive and require specialized administration, limiting their accessibility for many patients.[12,13]

Natural and plant-derived compounds have also garnered significant attention as potential alternatives. Polysaccharides derived from *Hippophae rhamnoides* L., for example, have demonstrated potent anti-inflammatory and antioxidant properties in preliminary studies, suggesting their potential as a safe and effective substitute for corticosteroids. Lifestyle interventions, including dietary modifications and stress management, may complement pharmacological approaches, particularly in managing chronic, low-grade inflammation.[14]

Prednisone usage contraindications (Table 1)

Sr. No.	Conditions	Reason
1	Hypersensitivity to prednisone	Individuals with a history of hypersensitivity to prednisone may experience severe allergic reactions, including anaphylaxis, necessitating alternative treatment strategies.
2	Infectious diseases	Prednisone can exacerbate infections, including eye infections, or lead to immune suppression. Patients exposed to shingles, chickenpox, or measles are at heightened risk of complications.
3	Pregnancy or breastfeeding	The teratogenic potential of corticosteroids, as well as concerns regarding excretion into breast milk, limits its use in pregnancy or lactating individuals.
4	Pre-existing medical conditions	Liver dysfunction, unhealed wounds, heart failure, hypertension and glaucoma are the conditions which can be exacerbated by prednisone.
5	Chronic diseases	Patients with diabetes, epilepsy, osteoporosis, stomach ulcers, or hypothyroidism may experience worsening symptoms.

Exploring alternatives to prednisone in Hypersensitivity pneumonitis

Types	Antigen Exposure	Onset of symptoms	Symptoms	Pathogenesis
Non-fibrotic HP	High-level intermittent exposure	Hours or days following significant exposure	Cough, dyspnea, fatigue, flu-like syndrome (fever, chills, malaise, cough, chest tightness, dyspnea & headache.)	Exposure to antigen followed by identification by dendritic cells. This activates immune complex (Type III hypersensitivity) and Cell mediated (Type IV hypersensitivity). This further increases neutrophils, mast cells, macrophages, CD8+T-cells & inflammatory cytokines.
Fibrotic HP	Low-level continuous exposure	Months after exposure	No apparent acute episodes. Progressive dyspnea, cough, fatigue, malaise and weight loss.	

Table 2. Clinical representation of hypersensitivity pneumonitis (HP) [15]

Given the limitations and risks associated with prednisone use, exploring alternative and adjuvant therapies for hypersensitivity pneumonitis has become a critical focus. Emerging therapies aim to reduce dependency on corticosteroids while addressing inflammation and preventing disease progression.

1. Biological therapies: These are a promising frontier for managing hypersensitivity pneumonitis. Targeted agents, such as monoclonal antibodies, can modulate specific inflammatory pathways without the systemic side effects. For instance, tumor necrosis factor-alpha (TNF-α) inhibitors and interleukin-6 (IL-6) blockers are being explored for their potential to attenuate immune responses. [15,16]

2. Antioxidant and natural compounds: Natural products, particularly plant-derived compounds, offer a safer and sustainable approach to managing the disease. Sea buckthorn have shown considerable promise due to their anti-inflammatory and antioxidant properties. These compounds may help mitigate oxidative stress and inflammation in lung tissues, addressing two key drivers of the disease pathology.
3. Pulmonary rehabilitation and supportive care: This includes exercise training, breathing techniques, and patient education which are vital for managing chronic hypersensitivity pneumonitis. These programs can improve lung function, reduce symptoms, and enhance quality of life. Additionally, oxygen therapy may alleviate hypoxemia, while antifibrotic agents under investigation could prevent or slow the progression of pulmonary fibrosis in advanced cases.[17]
4. Adjuvant therapies: Albuterol, Cetirizine, EGCG, and Pirfenidone adjuvant therapies play an essential role in complementing the effects of natural compounds like sea buckthorn, particularly in managing specific symptoms and pathological mechanisms of hypersensitivity pneumonitis:

- Albuterol: As a bronchodilator, albuterol helps relieve bronchoconstriction and improve airflow in patients with hypersensitivity pneumonitis, especially during acute exacerbations. While it does not directly reduce inflammation, its ability to alleviate respiratory symptoms makes it an important supportive therapy alongside anti-inflammatory agents.[18]
- Cetirizine: This antihistamine can reduce allergic responses and histamine-driven inflammation in hypersensitivity pneumonitis caused by antigen exposure. Its role as an adjuvant therapy can complement broader anti-inflammatory strategies, especially in patients with concurrent allergic conditions.[19]
- Epigallocatechin Gallate (EGCG): EGCG, a polyphenol derived from green tea, has shown potent anti-inflammatory and antifibrotic properties. In hypersensitivity pneumonitis, EGCG may help modulate immune responses and prevent fibrosis by inhibiting key signaling pathways involved in tissue damage. When used alongside sea buckthorn, it could enhance antioxidant defenses and provide additional protection against lung damage. [20]
- Pirfenidone: This antifibrotic agent is particularly useful in preventing or managing pulmonary fibrosis, a potential complication of chronic hypersensitivity pneumonitis. By reducing fibroblast proliferation and collagen deposition, pirfenidone addresses long-term structural damage in the lungs, making it a valuable adjunct to anti-inflammatory therapies.[21]

Role of sea buckthorn and plant-based therapies

Among plant-based alternatives, sea buckthorn has emerged as a particularly promising candidate for hypersensitivity pneumonitis. The berries have been found miraculous with immunomodulatory effects, reducing pro-inflammatory cytokine levels and oxidative stress. By addressing both inflammation and oxidative damage, sea buckthorn offers a dual-action mechanism that could significantly benefit patients. Moreover, its safety profile makes it an attractive option for long-term use, either as a standalone therapy or in conjunction with other treatments. The compounds like quercetin, flavonoids and other polyphenols derived from sea buckthorn hold potential for alleviating symptoms and reducing reliance on corticosteroids. Future research can be based on the focus standardizing these compounds, optimizing their dosages, and conducting clinical trials to establish their efficacy and safety with other treatments.

Mechanism of Action

Sea buckthorn berries and the adjuvants (albuterol, cetirizine, EGCG, and pirfenidone) can work synergistically to cure or prevent hypersensitivity pneumonitis.
1. *Hippophae rhamnoides* berries: The berries contain bioactive compounds like flavonoids, polysaccharides, carotenoids, and vitamins that modulate inflammation and oxidative stress. These mechanisms include:

a) Anti-inflammatory effects

- Inhibition of NF-κB pathway, a major transcription factor that promotes the release of pro-inflammatory cytokines (e.g. TNF-α, IL-6, IL-1β).
- Reduction in pro-inflammatory cytokines: It downregulates cytokines like TNF-α, IL-6, and IL-17, mitigating alveolar inflammation in HP. [22]

b) Antioxidant action

- Scavenging reactive oxygen species (ROS): Polyphenols and carotenoids neutralize ROS, which play a key role in oxidative stress-induced lung injury.
- Upregulation of Nrf2 pathway: The compounds activate Nrf2, which enhances the expression of antioxidant enzymes like glutathione peroxidase (GPx) and superoxidase dismutase (SOD). [23]

c) Immunomodulation

- Regulation of T-helper cells: Sea buckthorn polysaccharides help shift the immune response from a Th-1 dominant to a more balanced Th2/Th17 response, reducing hypersensitivity.
- Inhibition of Mast cell degranulation: By stabilizing mast cells, it reduces histamine release, alleviating allergic symptoms associated with HP. [24]

d) Prevention of fibrosis

- Suppression of TGF-β1 Signaling: TGF-β1, a key fibrotic mediator, is inhibited by sea buckthorn, preventing fibroblast activation and excessive collagen deposition in the lungs. [25]

2. Adjuvant therapies

a) Albuterol

- Bronchodilation: Albuterol activates β2-adrenergic receptors, leading to relaxation of bronchial smooth muscle and improved airflow.
- Reduced inflammatory markers: Albuterol indirectly reduces the release of pro-inflammatory mediators like leukotrienes and histamine by decreasing mast cell activation during acute exacerbations. [18]

b) Cetirizine

- Histamine blockade: As a H1 receptor antagonist, cetirizine reduces histamine-induced inflammation, bronchoconstriction, and vascular permeability.
- Inhibition of cytokines: Cetirizine lowers IL-4, IL-5, and IL-13 levels, which are associated with hypersensitivity and allergic inflammation. [19]

c) Epigallocatechin Gallate (EGCG)

EGCG, a green tea polyphenol, exhibits multiple anti-inflammatory and antifibrotic effects:

- Inhibition of TGF-β1/Smad pathway: EGCG prevents the activation of fibroblasts and reduces extracellular matrix production, mitigating lung fibrosis.
- Suppression of MAPK pathway: EGCG inhibits MAPK (ERK, JNK, p38), reducing the release of inflammatory cytokines.
- Antioxidant action: By scavenging ROS and enhancing Nrf2-mediated antioxidant defense, EGCG protects against oxidative lung injury. [20]

d) Pirfenidone

- Inhibition of TGF-β1 and TNF-α: Pirfenidone directly suppresses TGF- β1, reducing fibroblast activation and collagen synthesis. It also lowers TNF-α levels, dampening inflammation.
- Regulation of fibroblast activity: By inhibiting fibroblast proliferation and differentiation into myofibroblasts, pirfenidone prevents fibrotic remodeling of lung tissues.
- Reduction of ROS: Pirfenidone decreases ROS levels, protecting against oxidative stress-induced fibrosis. [21]

3. Combined Mechanisms and synergy

a) Reduction of inflammatory cascade

- Sea buckthorn + EGCG: Both target the NF-κB and MAPK pathways, leading to significant reductions in pro-inflammatory cytokines (e.g. TNF-α, IL-6, IL-1β). [20,24]
- Sea buckthorn + cetirizine: Sea buckthorn's mast cell-stabilizing effects complement cetirizine's histamine-blocking action, resulting in comprehensive control of allergic inflammation. [19,24]

b) Enhanced antioxidant defense

- Sea buckthorn + EGCG + Pirfenidone: The combined activation of the Nrf2 pathway and reduction of ROS provides robust protection against oxidative damage to lung tissues. [20,21,24]

c) Fibrosis prevention

- Sea buckthorn + EGCG + Pirfenidone: These therapies converge on the inhibition of the TGF-β1 pathway, effectively preventing fibroblast activation and collagen deposition. [20,21,24]

d) Improved lung function

- Sea buckthorn + Albuterol: While sea buckthorn reduces inflammation and oxidative stress, albuterol ensures immediate relief from bronchoconstriction, enhancing oxygen exchange and reducing dyspnea. [18,24]

4. Molecular pathway interaction

a) NF-κB pathway: Inhibited by sea buckthorn, EGCG, and pirfenidone, reducing cytokine -mediated inflammation. [26]
b) MAPK pathway: Suppressed by EGCG and pirfenidone, mitigating the release of pro-inflammatory mediators. [27]
c) Nrf2 pathway: Activated by sea buckthorn, EGCG, and pirfenidone, enhancing antioxidant defenses. [28]
d) TGF-β1 pathway: Blocked by sea buckthorn, EGCG, and pirfenidone, preventing fibrosis. [28]
e) Histamine pathway: Blocked by cetirizine, complemented by sea buckthorn's mast cell stabilization.

Replacing corticosteroid

Replacing corticosteroids like prednisone in case of hypersensitivity pneumonitis involves utilizing alternative therapies that can mimic prednisone's anti-inflammatory and immunosuppressive effects while reducing the associated adverse effects. The anti-inflammatory effects, immunomodulation, antioxidant defense, prevention of fibrosis, and symptomatic relief suggest that the adjuvant therapies and sea buckthorn berries could collectively substitute prednisone as a therapeutic strategy for HP.

Advantages over prednisone

Unlike prednisone, these alternatives are not associated with severe side effects like osteoporosis, hyperglycemia, or immunosuppression. The combination of sea buckthorn and adjuvants targets multiple pathways (inflammation, oxidative stress, fibrosis), offering a broader therapeutic profile. Natural compounds like sea buckthorn and EGCG are safer for prolonged use, making them suitable for chronic conditions like HP. Also, there are several withdrawal symptoms associated with prednisone use such as fatigue, weight loss, nausea, dizziness, vomiting, diarrhea and abdominal pain which can be avoided with natural compounds.

Practical replacement strategy

- Initial therapy: For acute exacerbations, a combination of albuterol (bronchodilation) and cetirizine (anti-allergic) can manage immediate symptoms while sea buckthorn, EGCG, and pirfenidone work on the underlying inflammation and fibrosis.

- Maintenance therapy: Long-term use of sea buckthorn berries (anti-inflammatory and antioxidant), EGCG (antioxidant and antifibrotic), and pirfenidone (antifibrotic) can replace the chronic use of prednisone.
- Monitoring and adjustments: Pulmonary function tests and imaging should be used to monitor lung health, with therapies adjusted based on disease progression and symptom control.

Conclusion

Prednisone's limitations and associated risks call for the development of safer, more effective alternatives to manage hypersensitivity pneumonitis and similar inflammatory conditions. Sea buckthorn, with its immunomodulatory and antifibrotic properties, presents a promising natural substitute. The combination of sea buckthorn with adjuvants like albuterol, cetirizine, EGCG, and pirfenidone addresses inflammation, oxidative stress, and fibrosis through multi-pathway interactions, providing comprehensive therapeutic benefits. The integrated approach not only reduces dependency on corticosteroids but also enhances patient safety and long-term disease management. Future research should focus on standardizing natural compounds, optimizing dosage, and conducting clinical trials to establish their efficacy as sustainable therapeutic options.

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