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Checkpoint Inhibitor Pneumonitis: Updates in Management

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ABSTRACT

Checkpoint inhibitor pneumonitis (CIP) is a potentially life-threatening immune-related adverse event associated with immune checkpoint inhibitors (ICIs). While high-dose corticosteroids remain the first-line treatment, up to 40% of patients experience steroid-refractory or resistant disease, posing significant management challenges. This review synthesizes current evidence on evolving CIP management strategies, highlighting both established therapies and emerging options. Recent guidelines favor mycophenolate mofetil (MMF) and intravenous immunoglobulin (IVIG) as second-line agents, replacing infliximab due to infection concerns in this immunocompromised population. Additional therapies such as cyclophosphamide, calcineurin inhibitors, and pulsed-dose corticosteroids have shown benefit in select cases, though evidence remains limited. Advances in understanding CIP immunopathogenesis have spurred interest in targeted biologics, notably interleukin-6 inhibitors like tocilizumab, which demonstrate promise in early reports. Antifibrotic agents, including nintedanib and pirfenidone, are also under investigation for their potential to manage fibrosis, particularly in patients with underlying interstitial lung disease or progressive fibrotic changes. Experimental strategies such as plasmapheresis, granulocyte-macrophage colony-stimulating factor (GM-CSF) modulation, and Janus kinase (JAK) inhibitors are being explored, with several prospective trials underway. Despite these advances, challenges persist in early diagnosis, risk stratification, and the absence of prospective, biomarker-driven treatment algorithms. This review emphasizes the importance of multidisciplinary, individualized management and highlights promising avenues for future research to improve outcomes in this increasingly encountered complication of cancer immunotherapy.

Introduction

The advent of immune checkpoint inhibitors (ICIs) has revolutionized cancer treatment, particularly for malignancies with poor prognostic outcomes. The mechanism of action of ICIs allows them to target inhibitory pathways that regulate T-cell activation. These agents then restore and enhance the immune system's ability to recognize and eliminate tumor cells. Programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors are among the most extensively studied and widely used ICIs, demonstrating significant efficacy in treating various malignancies, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, and urothelial carcinoma[1,2]. However, despite their therapeutic benefits, ICIs can lead to immune-related adverse events (irAEs), with checkpoint inhibitor pneumonitis (CIP) emerging as a potentially life-threatening toxicity[3,4].

PD-1 and PD-L1 inhibitors function by disrupting the interaction between PD-1 receptors on T cells and PD-L1 expressed on tumor and antigen-presenting cells. This inhibition prevents immune evasion by malignant cells, thereby enhancing T-cell-mediated cytotoxicity[5]. While this mechanism is beneficial for tumor eradication, it can also lead to an unregulated immune response against self-antigens, resulting in inflammatory toxicities such as pneumonitis[6]. The incidence of CIP varies across different malignancies, with NSCLC patients facing the highest risk due to pre-existing lung damage and chronic inflammation from smoking-related lung disease or prior radiation therapy[7,8].

Several risk factors contribute to the development of CIP, including patient-specific and treatment-related variables. Pre-existing interstitial lung disease, a history of radiation therapy, smoking, and prior pulmonary infections have been identified as significant predispositions[9,10]. Additionally, the combination of ICIs with chemotherapy or other immunomodulatory agents further increases the risk of pneumonitis[11]. Given the potential severity of CIP, early recognition and prompt management are crucial to improving patient outcomes. Current treatment strategies primarily involve corticosteroids, though steroid-refractory cases may require additional immunosuppressive therapies such as infliximab, intravenous immunoglobulin, or Tocilizumab[12-14].

This paper aims to provide a comprehensive discussion on checkpoint inhibitor pneumonitis, particularly new and emerging management strategies, to enhance clinical awareness and optimize treatment approaches in this complex irAE.

Pathophysiology and Clinical Features:

CIP results from dysregulation of the immune system due to the action of immune checkpoint inhibitors such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 monoclonal antibodies. It involves excessive activation and amplification of cytotoxic T lymphocytes and helper T cells, downregulation of regulatory T cells, and over-secretion of pro-inflammatory cytokines. Additionally, the dysregulation of innate immune cells, including inflammatory monocytes, dendritic cells, neutrophils, and M1 macrophages, contributes to inflammation of normal lung[15,16]. The increase in autoantibodies and cross-antigen reactivity also plays a role in the development of CIP[17].

CIP can present with nonspecific respiratory symptoms such as dyspnea, cough, and fever, which can resemble infectious pneumonia or other inflammatory lung conditions[6]. The onset of symptoms varies and can occur weeks to months after initiating ICIs[3]. Radiographically, CIP manifests in several distinct patterns on chest imaging, including ground-glass opacities, patchy nodular infiltrates, and organizing pneumonia. These patterns are often seen in the lower lobes and can be bilateral[18]. Other radiographic subtypes include hypersensitivity pneumonitis, interstitial pneumonitis, and acute interstitial pneumonia-acute respiratory distress syndrome[19].

The severity of CIP is graded using the Common Terminology Criteria for Adverse Events (CTCAE)

and helps to direct optimal management strategy (Table 1)[18].

Table 1: Common Terminology Criteria for Adverse Events (CTCAE) grading definitions

CTCAE Grade	Clinical severity
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated; limiting instrumental activities of daily living (ADLs)
3	Severe symptoms; limiting self-care ADLs; not immediately life-threatening; oxygen indicated as well as hospitalization
4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheostomy or intubation).
5	Fatal pneumonitis

Standard First-Line Management of Checkpoint Inhibitor Pneumonitis

CORTICOSTEROIDS:

Corticosteroids are the mainstay of treatment for checkpoint inhibitor pneumonitis. Current guidelines from the 2025 National Comprehensive Cancer Network (NCCN) and the 2021 clinical practice guidelines of the Society for Immunotherapy of Cancer (SITC) recommend initiating corticosteroid therapy based on the severity of pneumonitis. For grade 1 CIP, observation with close monitoring is appropriate. For grade 2 pneumonitis, oral prednisone (1-2 mg/kg/day dosing) or intravenous (IV) methylprednisolone (1-2 mg/kg/day dosing) is recommended. In cases of severe pneumonitis (grades 3-4), IV methylprednisolone at higher doses (1-2 mg/kg/day) may be initiated, with subsequent transition to oral prednisone as the patient stabilizes[20].

The duration of corticosteroid therapy follows a tapering schedule to minimize the risk of recurrence. Typically, an initial response is evaluated after 48-72 hours, and if improvement is observed, steroids are gradually tapered over 4-8 weeks, per NCCN guidelines[18]. In situations where there is decline with decreasing steroid dose, it can be increased to the most recent effective dose, with slower taper extended up to three months, per NCCN and American Society of Clinical Oncology clinical practice guidelines. In cases of refractory pneumonitis, pulsed-dose corticosteroids (methylprednisolone 500-1000 mg IV daily for 3 days) may be considered, but will be discussed in more detail later[13,21,22].

Guideline recommendations for the management of CIP emphasize early intervention with corticosteroids. The SITC and American Society of Clinical Oncology (ASCO) guidelines highlight that corticosteroids should be initiated promptly in symptomatic patients to prevent progression to respiratory failure[18,23]. The European Society for Medical Oncology (ESMO) guidelines also stress the importance of corticosteroid therapy while considering the use of immunosuppressive agents in refractory cases[24]. Studies have shown that early initiation of corticosteroids correlates with improved outcomes, whereas delayed therapy can lead to worse prognosis and prolonged hospitalization.[26,27]

The response to corticosteroids varies among patients with CIP. The majority of patients with grade 2 pneumonitis respond well to corticosteroid therapy, with symptom resolution within weeks[18,20]. However, patients with grade 3-4 pneumonitis have a higher risk of prolonged hospitalization, respiratory failure, and mortality despite corticosteroid treatment[25]. Factors associated with poor prognosis include

older age, preexisting lung disease (e.g., chronic obstructive pulmonary disease or interstitial lung disease), higher baseline inflammatory markers, and delayed initiation of steroids[26].

SUPPORTIVE CARE MEASURES:

Supportive care plays a crucial role in managing CIP. Patients with hypoxemia should receive supplemental oxygen therapy to maintain adequate oxygenation.

Empiric broad-spectrum antibiotics may be considered if secondary infection is suspected, particularly in cases of severe pneumonitis where differentiating between infection and immune-related inflammation is challenging[27]. In fact, for grade ≥2, disease, bronchoscopy and bronchoalveolar lavage can support the diagnosis of CIP and/or establish presence of infection[17]. If longer term steroids or other immunosuppression are required, particularly with low absolute lymphocyte counts, trimethoprim and sulfamethoxazole can be considered for Pneumocystis jirovecii prophylaxis[28]. The role of fluconazole prophylaxis for prolonged steroid need is even less well defined[29].

While there are no robust studies directly evaluating bronchodilator or pulmonary rehabilitation strategies in CIP, their use is often extrapolated from other pulmonary conditions such as COPD and interstitial lung disease, where they have been shown to improve respiratory function and quality of life[30]. In intensive care settings, mechanical ventilation can be used for some cases of severe respiratory failure, ensuring adequate conversations about patient and family preferences[27]. Veno-venous extracorporeal membrane oxygenation (VV-ECMO) has been utilized in a very limited capacity in published case reports, with good outcomes. However, appropriate patient selection is essential[18,27,31].

Management of Steroid-Refractory CIP

Despite appropriate corticosteroid and supportive therapies, a subset of patients develops steroid-refractory pneumonitis.

Steroid-refractory CIP is typically defined as a failure of response to steroid treatment within 48–72 hours or relapse of CIP despite initial response to steroids[25,26]. Incidence range from multiple studies is variable, between 2-18.5%, with the highest reported as 43% of CIP cases[6,25,26,32]. Steroid-refractory patients may have earlier onset and more severe pneumonitis, with less chance for durable treatment response[33]. It is associated with higher mortality as well, ranging from 35% up to 100%[3,6,25].

Several risk factors for refractory CIP exist, including history of interstitial lung disease, high CTCAE grade (3-4) at diagnosis, higher absolute neutrophil count, higher procalcitonin, lower albumin, and higher lactate dehydrogenase (LDH) levels[25,26]. Diffuse alveolar damage (DAD) has been observed to be a more common radiographic pattern for refractory CIP[6].

Various immune-modulating agents have been used in addition to steroids in the treatment of refractory CIP. Guideline recommendations for management of steroid-refractory CIP are largely based on retrospective studies, case studies and case series due to the low overall incidence of this disease. Currently infliximab, mycophenolate mofetil (MMF), and intravenous immunoglobulins (IVIG) are recommended by all four international consensus guidelines (European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), Society for Immunotherapy of Cancer (SITC), and National Comprehensive Cancer Network (NCCN)[3,18,20,24,32,34]. The rationale for use of these agents was initially derived from ILDs, autoimmune diseases and other irAEs.

INFLIXIMAB:

Infliximab is a monoclonal antibody targeting tumor necrosis factor α, resulting in decreasing proinflammatory cytokines (e.g., IL-1, IL-6) and thus acting as an immunosuppressant. It is administered at an initial dose of 5 mg/kg, with a follow-up dose at 14 days depending on clinical response.

Though infliximab has the most available evidence in irAEs, particularly colitis, data demonstrating

benefit in CIP has been inconsistent. Daetwyler et al. published a systematic review including 17 prior publications on refractory CIP who received infliximab revealed overall response rates of 25-33%[1,3,35]. In Beattie and colleagues' study of 26 patients with steroid-refractory or steroid-resistant CIP, addition of immunosuppression with Infliximab and/or mycophenolate mofetil, resulted in durable improvement in 38% of patients, and complete resolution, allowing for cessation of immunosuppression, in 12% of these individuals[3]. Additional cases of successful treatment of CIP with Infliximab have been reported, including in the setting of mycophenolate mofetil resistance[36,37]. However, Balaji et al.'s retrospective review studied 12 patients with refractory CIP, treated with infliximab monotherapy (n=2), IVIG monotherapy (n=7), and combined infliximab and IVIG (n=3)[6]. All patients who received infliximab died from pneumonitis or infectious complications (n=5)[6]. In another study, 312 patients with ≥ grade 3 irAEs managed with Infliximab + steroids vs. steroids alone demonstrated decreased survival with Infliximab[38]. Thus, Infliximab use in CIP requires larger studies to more definitively evaluate its benefit[6].

MYCOPHENOLATE MOFETIL (MMF):

Mycophenolate mofetil (MMF) immunosuppresses by reducing lymphocyte proliferation. Though its action is somewhat delayed, and thus less than optimal for acute CIP, it serves as a steroid-sparing agent. It is dosed at 1-1.5g between twice and thrice daily. Data for use in CIP is extrapolated from its efficacy in other ILDs, notably systemic sclerosis-associated ILD and fibrotic hypersensitivity pneumonitis[39,40]. Case reports suggest it can cause resolution of CIP in steroid-refractory situations with ground glass predominant imaging[41]. Beatie et al. demonstrated effectiveness of MMF in 5 out of 6 steroid-refractory CIP patients (83%) who demonstrated durable response at 8 weeks follow-up, compared with infliximab which resulted in durable response in only 4 out of 20 patients (20%)[3]. Nevertheless, caution must be exercised, as this was a single-center retrospective study and overall outcomes in steroid-refractory CIP remain poor, and resolution with ability to discontinue immune suppression is rare[3].

INTRAVENOUS IMMUNOGLOBULIN:

IVIG is pooled plasma of predominantly monomeric IgG derived from healthy donor plasma that can treat a range of autoimmune conditions by neutralization of pathogenic autoantibodies and suppression of immune activation[42]. Dosing is administered as a total of 2g/kg in daily divided doses over 2-5 days[27,34,42]. IVIG use in CIP is based on successful management of other irAEs such as myasthenia gravis, and some connective tissue disease associated ILDs[43]. Petri et al. report a case of steroid-refractory CIP in an intubated patient receiving pembrolizumab for metastatic lung adenocarcinoma, who had rapid and significant radiographic followed by clinical improvement with IVIG[43]. Balaji and colleagues found that with IVIG therapy in steroid-refractory CIP, two patients sustained improvement in disease grade (from 3 to 2), another two had stable grade disease, and three patients worsened to grade 5[6]. While these small reports have variable clinical outcomes with IVIG use, IVIG may pose particularly beneficial in steroid-refractory CIP with concurrent infection, as it is less immunosuppressive than other treatment options[16].

In the most recently published NCCN guidelines from 2025, IVIG and MMF are both preferred over infliximab for Grade 3 and 4 CIP[34].

CYCLOPHOSPHAMIDE:

Cyclophosphamide is an alkylating agent that prevents DNA cross-linking and decreasing DNA synthesis. It is well known to exert inhibitory effects on T-cell proliferation, while also promoting induction of suppressor T-cells, and is used in various contexts including other irAEs, interstitial lung disease and prevention of graft-versus-host disease[42,44,45]. Its role in refractory CIP is not well established, but there have been reports of successful treatment with cyclophosphamide. A retrospective multi-center registry review by Camard et al. in 2022 identified 6 patients with steroid-refractory CIP who were treated with cyclophosphamide (n=4), infliximab

(n=1), or IVIG (n=1). Though the mortality rate was high at 67% (i.e., 4/6 patients), the 2 surviving patients both received cyclophosphamide[46].

CALCINEURIN INHIBITORS:

Calcineurin inhibitors, such as tacrolimus and cyclosporine, target IL-2 release and inhibit T-cell activation, and have been reported in use for treatment of other ICI related adverse effects, such as colitis[33,47]. Evidence for calcineurin inhibitor use in refractory CIP remains extremely limited. Utsumi et al. published a case report of successful CIP treatment with a combination regimen of corticosteroids, tacrolimus, and cyclophosphamide[48]. Deng et al in 2024, published a case of successful treatment with cyclosporine in refractory CIP[49].

Emerging and Alternative Therapies

As the understanding of CIP continues to evolve, emerging and alternative therapies are being explored to improve treatment outcomes, particularly in steroid-refractory cases.

PULSED-DOSE CORTICOSTEROIDS:

An adaptation of steroid therapy is the use of pulsed-dose steroids (sometimes called "pulse corticosteroid therapy"). This involves short courses of very high steroid doses (e.g., methylprednisolone 500–1000 mg IV daily for 3 days) as rescue therapy in severe cases. Recent reports suggest pulse therapy may salvage patients who fail standard-dose steroids. Lai et al., for example, described two cases of grade 4 CIP that were refractory to 2 mg/kg methylprednisolone but improved rapidly after three days of 500 mg methylprednisolone pulses[13]. In both cases, respiratory failure reversed within 1–2 weeks of pulsed-dose steroid therapy[13]. Notably, a 2020 meta-analysis on pulse steroids in autoimmune diseases found that high-dose pulses did not significantly increase adverse effects compared to lower doses, suggesting they can be safely used in critical situations [21,27]. Early case-level evidence indicates that pulsed-dose steroids can be effective when standard steroid dosing is insufficient, even in cases of steroid-refractory CIP, before considering other immunosuppressants.

IL-6 INHIBITION (TOCILIZUMAB):

Interleukin-6 (IL-6) plays a central role in the pathogenesis of irAEs, including checkpoint inhibitor pneumonitis, by amplifying inflammation through Th17 polarization, suppression of regulatory T-cells, and activation of pro-inflammatory monocytes and macrophages[14]. In CIP, IL-6 contributes to pulmonary injury by promoting immune cell infiltration, increasing vascular permeability, and driving fibrosis. Elevated IL-6 levels in bronchoalveolar lavage fluid and blood correlate with irAE severity and steroid-refractory state[50]. These findings support the therapeutic use of IL-6 inhibitors like tocilizumab, which has shown promise in managing steroid-refractory CIP by targeting this key inflammatory pathway[51,52]. Tocilizumab, dosed at 4 mg/kg intravenously for irAEs, is a biologic agent originally used for rheumatoid arthritis and cytokine release syndrome[50]. In the context of CIP, tocilizumab has shown promise in retrospective analyses. A recent analysis of 87 patients with various irAEs on nivolumab included 12 patients with immune-related pneumonitis who received tocilizumab[12,53-55]. Clinical improvement was noted in most of these cases[12]. Overall, 27 of 34 patients treated with tocilizumab for various irAEs (including CIP) showed improvement[12]. There are also individual case reports describing successful rescue of steroid-refractory CIP with tocilizumab[52,56]. On the strength of this emerging evidence, some guidelines (e.g., NCCN and SITC) have started to list tocilizumab as a possible option for steroid-refractory pneumonitis. While no RCT data exist yet, IL-6 inhibition is an exciting new avenue. Ongoing collection of real-world data may further clarify its efficacy in CIP.

ANTIFIBROTIC THERAPY (NINTEDANIB AND PIRFENIDONE):

Nintedanib is a potent small molecule inhibitor of the receptor tyrosine kinases (including platelet-derived growth factor receptor, fibroblast growth factor receptor and vascular endothelial growth factor receptor) approved for idiopathic pulmonary fibrosis (IPF), systemic sclerosis ILD and progressive pulmonary fibrosis[57-60]. The rationale for nintedanib

in CIP stems from its anti-fibrotic, anti-inflammatory, and anti-tumor properties, which might counteract the organizing pneumonia or fibrosis that can occur in severe CIP with underlying malignancy[61]. Xie et al. reported a patient with advanced NSCLC who developed pembrolizumab-induced pneumonitis with elevated fibrosis marker Krebs von den Lungen-6 (L-6), restrictive physiology and abnormal chest tomography[61]. The addition of nintedanib to his steroid regimen led to clinical and radiographic improvement[61]. Yamakawa et al. described nintedanib added to prednisolone in an individual with pre-existing IPF and prior pembrolizumab CIP, who was starting atezolizumab[62]. The patient remained stable, without pneumonitis, suggesting possible preventive benefit[62].

Pirfenidone is approved for use in IPF, based on its ability to slow progression of disease via inhibition of the TGF-β pathway as well as other less well-defined actions[63]. Retrospective data of 15 CIP patients treated with Pirfenidone + steroids vs. 30 patients treated with steroids alone revealed significant improvement in forced vital capacity, diffusion capacity, six-minute walk test and pulse oximetry (without supplemental oxygen), with good safety profile[64]. Yu et al. presented a case of CIP managed with initial pulsed-dose steroids followed by 11 months of Pirfenidone, with improved clinical and radiologic findings[65]. Additionally, Maio and colleagues were able to demonstrate reduced dyspnea and improved hypoxemia (to 5 liters/minute) in a case of CIP, though the patient's recent prior treatment with tocilizumab, steroids, and IVIG complicate evaluation of Pirfenidone's particular benefit in this paper[66].

The examples above are anecdotal but intriguing. They raise the question of whether antifibrotics could serve as adjunctive therapy in chronic or non-resolving CIP, especially where lung fibrosis is evident. Notably, unlike immunosuppressants, nintedanib and pirfenidone do not carry infection risk, and have anti-tumor properties, making them particularly attractive options for CIP management[67,68].

OTHER EXPERIMENTAL INTERVENTIONS:

Additional experimental treatments have been tried in isolated cases.

Plasmapheresis has been used in severe irAEs (though more so for neurologic toxicities such as Guillain-Barre and myasthenia gravis) and might be considered if an immune-complex–mediated process is suspected in CIP[69]. By clearing pro-inflammatory cytokines, chemokines, pathogenic antibodies, and ICIs, plasmapheresis may stop irAE progression and possibly even reverse it[70].

Granulocyte-macrophage colony-stimulating factor (GM-CSF), such as sargramostim, may reduce immune-related adverse events by promoting regulatory myeloid cells, supporting tissue repair, and modulating inflammatory cytokines, such as IL-6 and TNF-α[71]. For GI irAEs, sargramostim may help prevent this condition without impairing anti-cancer therapy[72]. Hodi et al, in their multicenter, randomized study, demonstrated that ipilimumab combined with sargramostim, in advanced melanoma, helped balance immune activation, leading to improved overall survival and reduced immune-related adverse events, including pneumonitis[73]. This implies a potential protective role of GM-CSF against pulmonary toxicity[73].

Inhibition of Janus kinase (JAK) signaling pathway is another modality for managing irAEs, that may also be applicable to CIP patients. The JAK signaling pathway appears to be upregulated in irAEs, and case reports of JAK inhibitors used to successfully treat ICI related myocarditis, colitis, and neurologic disease, imply a similar benefit in CIP. NCT05899725, is a prospective multicenter randomized controlled interventional study that is currently recruiting. It aims to investigate the addition of Ruxolitinib, a JAK 1/2 inhibitor, to corticosteroid therapy in patients with severe (grade 3–4) CIP[74]. Scheduled for completion in 2025, this study will evaluate corticosteroid-sparing effects, mortality, need for mechanical ventilation, and infection rates[74].

In addition, NCT06860542 is a Phase II trial, entitled Inhaled Budesonide for REcurrence Prevention and Adjuvant THerapy in Checkpoint Inhibitor Pneumonitis (*IBREATHCIP*), will help determine whether the use of inhaled budesonide for 36 weeks following an initial CIP episode can reduce the risk of both refractory and recurrent pneumonitis[75]. This trial will also assess reductions in systemic steroid exposure, steroid-related toxicity, and improvements in patient-reported outcomes[75].

Overall, these emerging and alternative therapies offer potential options for managing CIP, particularly in cases refractory to standard corticosteroid treatment. Further research and larger clinical trials are necessary to more comprehensively establish therapeutic regimens with optimal efficacy and safety profiles.

Rechallenge and Prevention Considerations

The decision to rechallenge patients with immune checkpoint inhibitor therapy after an episode of checkpoint inhibitor pneumonitis remains complex, requiring careful balancing of the risks of recurrence against potential benefits in cancer control. Studies suggest that while rechallenge is feasible in select cases, recurrence of pneumonitis occurs in up to 28% of patients[11]. Risk factors for recurrence include higher-grade initial pneumonitis and shorter intervals between symptom resolution and rechallenge[4]. Despite the risks, a rechallenge may be associated with prolonged oncologic benefit in patients who respond favorably to immunotherapy, underscoring the need for careful patient selection[3].

Current clinical guidelines recommend a cautious approach to ICI rechallenge. According to ASCO, ESMO, and NCCN guidelines, patients with grade 1–2 CIP may be considered for rechallenge following full resolution of symptoms and completion of a steroid taper, provided the risks and benefits are thoroughly discussed with the patient[23]. Rechallenge is generally discouraged in cases of grade 3–4 CIP unless the patient has no alternative treatment options, on a case-by-case basis with shared decision making.

Prevention strategies are essential, particularly for patients at high risk of developing or recurring CIP. Close radiographic and clinical monitoring is recommended during and after immunotherapy initiation, especially in patients with pre-existing interstitial lung disease or prior thoracic radiation[7,9]. Emerging data suggest that antifibrotic agents such as nintedanib or pirfenidone may play a role in mitigating pulmonary fibrosis following CIP, particularly in patients with pre-existing fibrotic lung disease or radiologic features of progression[61]. Inhaled corticosteroids are also under investigation, with the IBREATHCIP trial evaluating inhaled budesonide to prevent recurrent or refractory CIP in patients recovering from an initial episode[75]. Ongoing trials such as the study of pirfenidone in combination with methylprednisolone, by Chengzhi at the Guangzhou Institute of Respiratory Disease, may provide further insight into this potential strategy[76].

Rechallenge with ICIs post-CIP must be individualized, with multidisciplinary collaboration, rigorous monitoring, and informed consent. Prophylactic measures, including infection prevention and possibly antifibrotic therapy, may reduce the risk of severe recurrent toxicity in vulnerable populations.

Conclusion

The management of checkpoint inhibitor pneumonitis continues to evolve. While corticosteroids remain the first-line treatment, the need for more effective second-line therapies has become increasingly evident, particularly for patients with steroid-refractory disease. The development of prospective trials and collaborative registries will be critical in refining treatment strategies and improving outcomes for this potentially devastating disease.

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