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PIRFENIDONE: A NOVEL POTENTIAL THERAPEUTIC AGENT IN THE MANAGEMENT OF CHRONIC ALLOGRAFT REJECTION

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Abstract:

Chronic allograft dysfunction is a leading cause of allograft failure, morbidity and mortality following solid organ transplantation. The pathogenesis of chronic allograft failure has a final common pathway leading to organ fibrosis. Pirfenidone is an effective and novel anti-fibrotic agent with anti-inflammatory properties. Clinical use of the agent has been tested in a number of non-transplant recipients and has a favorable safety profile based on available clinical data. Building on these observations and findings, and considering the role of fibrosis in chronic allograft rejection, Pirfenidone (PFD) was initially investigated as adjunctive therapy in a rat heterotopic tracheal transplantation model. This led to several studies which confirmed that PFD may well be worth considering for further investigation. This paper reviews the possibility of using PFD in clinical transplantation management.

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The process of fibrosis, a common endpoint in chronic graft dysfunction, can be divided into three stages: 1) an initial inflammatory response, 2) tissue injury and 3) subsequent restoration and repair. PFD may help to limit these aspects of the fibrotic response (1). Pirfenidone has actions that suppress $\text{TNF}\alpha$, a key regulator of the inflammatory response in allograft rejection. In addition, PFD's direct action in $\text{TGF}\beta$ expression, even after transcription is activated, is another cellular effect which could have possible beneficial clinical consequences in the transplantation setting (1).

Mechanism of Action:

Pirfenidone, 5-methyl-1-phenyl-2(1H)-pyridine, is a nonpeptide low molecular weight agent with oral bioavailability (Figure 1). Oral absorption is estimated at 80% and the serum half life is 2-3 hours. PFD's actions as an anti-fibrotic agent are attributable to its inhibition of p38-gamma MAP kinase. In addition, PFD may regulate translational silencers such as TIA-J (2). The result is an inhibition of fibrotic factors most notably, $\text{TGF}\beta 1$. As a consequence, downstream synthesis of extracellular matrix proteins, such as fibronectin, elastin and collagen are reduced. Other studies have also elucidated the ability of PFD to scavenge oxygen radicals, to decrease NO production and to down regulate arginase, an enzyme induced by $\text{TGF}\beta$ and involved in collagen synthesis (3, 4).

Based on these mechanisms of action and the pathophysiology of chronic allograft dysfunction, which includes activation of fibrosis pathways, the goal of this paper is to

review the transplantation and non-transplantation literature for evidence that PFD may be a future consideration for study in the setting of clinical lung transplantation.

Methods and Materials:

The literature base of the NIH library was systematically reviewed to update current knowledge of the compound PFD, relative to the pathophysiology of transplant related bronchiolitis obliterans syndrome. These areas included: 1) PFD cellular proliferation studies, 2) testing of PFD in transplantation and injury in vivo models, 3) human Clinical Trials utilizing PFD as an anti-fibrotic agent and 4) PFD interactions with the calcineurin inhibitors. Studies were selected for inclusion in this article, and the results were described if there was a link to available cellular and in vivo data on lung allograft dysfunction.

Results:

Proliferation Studies:

The role of PFD as an anti-fibrotic agent has been well established in several studies. In chronic lung allograft dysfunction or Obliterative Bronchiolitis, fibrosis of the airway lumen follows epithelial denudation. In studies conducted on human lung fibroblasts, PFD slowed proliferation in a dose dependent manner. Lung fibroblasts grown in the presence of conditioned media from bronchial epithelial cells slowed their proliferative response to PFD. This effect appeared to be related to the increase in cellular apoptosis in the G1/G0 phase of cell growth (5, 6). Similarly, in vitro studies of rat renal fibroblasts showed that PFD effects proliferation and activation (7).

Attenuation of Ischemia and Reperfusion Injury:

Pirfenidone has been used in several animal models of ischemic-reperfusion injury. These studies indicate that PFD lowers TNF concentrations in tissue. This reduction of local expression of TNF correlated with reduction of tissue damage, edema and hypotension (8).

In a rat model of partial hepatic ischemia, PFD at a dose of 300mg/kg was administered following LPS. The results indicated that there were lower liver enzyme levels after reperfusion and lower cytokine-induced neutrophil chemoattractants in both serum and liver tissue (9). The local and systemic effects of PFD in minimizing the damage from ischemic-reperfusion injury, may have implications for acute transplantation injury as well. Acute graft injury and rejection is one of the major risk factors for development of BOS.

Anti-Inflammatory Actions:

Cellular studies indicate that PFD results in lower expression of pro-inflammatory cytokines in both conditioning media and cell lysate. In one study of murine macrophages, TNF responses to LPS treatment were attenuated by application of PFD in a dose dependent manner. The authors found that in their cellular model this effect was independent of the MAPK2 system (10). In other studies, PFD has been suggested to enhance IL-10, an anti-inflammatory cytokine at the transcriptional level (11).

Use as an Anti-Fibrotic Agent:

PFD has been established as an anti-fibrotic agent in several in vivo studies. In one study of hamsters, PFD was administered before and during intra-tracheal bleomycin

instillation. PFD was found to be most effective if given prior to the induction of lung fibrosis (12). Similarly, in a renal fibrosis model using vanadate, PFD was protective in limiting the severity of injury to the kidneys. There are several studies also indicating that PFD is useful in limiting or reversing cardiac fibrosis. (13). In addition, hepatic studies have indicated that administering rats PFD for 4 weeks following dimethylnitrosamine inhibited the development of fibrosis as assessed by pathology and tissue hydroxyproline content. PFD also decreased TGF β and collagen type I mRNA expression in this model (14, 15). In cirrhotic rats, PFD (500 mg.kg.day) reduced serum aminotransferase and alkaline phosphate levels as well as liver hydroxyproline content and fibrosis index scores (15, 16). Pirfenidone has the demonstrated effect of reducing fibrosis and the markers of extracellular matrix deposition in varied in vivo models. The optimal timing of PFD in relation to the injuring agent depends on the experimental model used.

In human clinical trials, PFD has been investigated as an anti-fibrotic therapeutic agent in diseases with a variety of target organs. PFD is under current study as a treatment for idiopathic pulmonary fibrosis (17, 18), familial adenomatous polyposis associated desmoid disease, and Hermansky-Pudlak syndrome (19, 20). In a recent open-label phase II study of 24 patients with Neurofibromatosis I, there was demonstrated efficacy in shrinking the size of the lesions (21). There is at least one case report of a non-transplant patient with bronchiolitis obliterans being successfully controlled by the addition of PFD to cyclosporine (CSA). The patient's steroid dose was able to be reduced (22).

PFD in Airway Transplantation Models:

Pirfenidone was initially investigated in a rat model of obliterative bronchiolitis using heterotopic tracheal transplantation. In this model the resultant airway lesion is indistinguishable from the histologic lesion of chronic progressive lung allograft rejection. In this study, the initial injury occurred in the first seven days after transplantation in the absence of CSA. Pirfenidone was given to recipient rats at a dose of 600 mg/kg/day of nearly continual administration. The results indicated that with the combined use of CSA and PFD the resultant lesion, was less organized and there was less fibrogenic potential and lower local production of TGF β , when compared to the monotherapy PFD and CSA groups. (23). Subsequently, McKane et al., used a murine heterotopic transplantation model without the use of an immunosuppressive agent. The mice receiving PFD (0.5%) early in the course versus later in the post-transplantation course, had delayed onset of luminal obliteration of the airway (24). The heterotopic tracheal transplantation model has its limitations though since the smaller airways are not transplanted. These studies established the use of PFD as a modifying agent in the setting of in vivo transplantation. A third study of heterotopic tracheal transplantation showed that animals receiving a combination of PFD and rapamycin had more protection against the development of obliteration, than either agent used alone. This effect was only seen if the PFD was administered early in the course, suggesting that in part PFD may be limiting early inflammatory damage to the epithelium (25). All three in vivo studies of PFD demonstrated that PFD is most effective when used early in the

course, suggesting its effect in limiting immune mediated and inflammatory triggers to fibrosis may be one possible cellular mechanism of its actions.

Liu et al, used PFD without an immunosuppressive agent, in an orthotopic lung transplantation model and the results indicated that PFD decreased lung allograft damage. The lungs at day 21 post-transplantation also were associated with lower lung myeloperoxidase enzymatic activity, and plasma tissue necrosis factor α (26).

The Favorable interaction between PFD and Calcineurin Inhibitors:

Calcineurin inhibitors are widely used in the management of transplantation patients. These agents have been associated with fibrotic gene induction and development of fibrosis in the transplanted organ.

There is current evidence that PFD used in combination with calcineurin inhibitors results in less extracellular matrix deposition. In two in vivo studies utilizing a salt depleted rat model of CSA nephrotoxicity the regulation of pro-fibrotic genes in the presence of PFD was investigated. The results indicated that in the rats receiving PFD, pro-fibrotic genes were down regulated. These genes included TGF β , TIMP-1, collagen III and there was less matrix deposition in the renal cortex (26-28). Further investigation may be warranted to elucidate the exact mechanisms of the drug interaction.

Clinical Safety Data:

Pirfenidone has been used to control a variety of fibrotic diseases in humans. It has been studied in particular in the treatment of idiopathic pulmonary fibrosis (IPF). In these trials, several patients treated with PFD developed adverse reactions, but these reactions did not result in significant morbidity, mortality or termination of their

participation. Among the adverse effects, GI symptoms , photosensitivity and anorexia were prominent among the drug group ($p, 0.05$, $n= 73$). However, overall the drug was well tolerated and did not significantly alter participation. PFD has also had a favorable safety profile in studies of multiple sclerosis and Herman-Pudlak syndrome. In these trials, patients treated with PFD did experience nausea, which was controllable by lowering the dose, and some patients experienced dizziness. Further large scale Phase III investigations are currently being conducted (15).

Discussion:

Pirfenidone is a novel anti-fibrotic and anti-inflammatory agent with specific cellular, biochemical and histologic effects which are worthy of consideration in the management of transplantation recipients. Chronic allograft dysfunction is associated with organ fibrosis and remains a problematic and often devastating occurrence in transplant patients.

The results of several investigations would indicate that when Pirfenidone is given early in the transplantation course and as an adjunctive agent, the potential exists that steroid dosing could possibly be lowered. Chronic allograft dysfunction may be better controlled in the presence of PFD, by preventing some of the early inflammatory reaction, and subsequent fibrosis of the organ.

Based on available drug safety data, there is currently no contraindication to administration of the drug. Adverse effects are largely not associated with discontinuation of the drug and can be managed by adjusting the dose.

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Figure Legend

Figure One

The Chemical Structure of Pirfenidone