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RESEARCH ARTICLE

CAN PIRFENIDONE BE A TREATMENT MODALITY IN ORAL SUB MUCOUS FIBROSIS?

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ABSTRACT

Oral submucous fibrosis (OSMF) is a potentially malignant collagen metabolic disorder affecting the oral cavity due to the imbalance in collagen production and breakdown mediated by transforming growth factor beta (TGF-β). Numerous modalities ranging from behavioural therapy, physiotherapy, steroids, enzymes, nutritional supplements, antioxidants, interferons, turmeric, ayurveda to various drugs have been tried with weak evidence requiring better documentation of the studies performed with standardized criteria. One drug perfinidone (5-methyl-1-phenyl-2-(1H) pyridine) a novel antifibrotic agent used extensively in lung, cardiac and liver fibrosis has still not been tried in OSMF. This drug mainly exerts it action blocking the action of TGF-β. A positive outcome with prolonged research and numerous clinical trials, evaluating the systemic and topical uses of pirfenidone in OSMF with can give a ray of hope to these patients, helping them achieve a better quality of life. This paper aims at proposing this drug in the treatment of OSMF which can be beneficial in managing this progressively debilitating disease, significantly improving quality of life.

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INTRODUCTION

Oral submucous fibrosis (OSMF) is a debilitating potentially malignant condition resulting from the deregulation in the collagen metabolism (Arakeri and Brennan, 2013). Numerous studies have established a dose dependant relation between areca nut and causation of OSMF (Tilakaratne *et al*., 2006; Auluck *et al*., 2008). Multiple aetiological factors including capsaicin in chillies, iron, zinc, and deficiencies in essential vitamins (Arakeri and Brennan, 2013; Tilakaratne *et al*., 2006) immunologic and genetic predisposition (Auluck *et al*., 2008) have also been considered. Clinically the disease progresses in stages with patients presenting with burning sensation, intolerance to spicy food, vesicles particularly on the palate, ulceration and dryness of the mouth, fibrosis of the oral mucosa, leading to lips, tongue, and palate rigidity and finally trismus (Arakeri and Brennan, 2013; Auluck *et al*., 2008) Annually 0.5% of OSMF cases become malignant (Isaac van der Waal, 2009). Physical therapy, antioxidants, steroids, immunological modulators like interferon gamma, fibrinolytic agents like hyaluronidase, collagenase, ayurvedic treatment with turmeric, green tea and many drugs like pentoxiphylline, buflomedil hydrochloride, nylidrin, have been used to manage OSMF. Surgical line of treatment including extra oral and intraoral flaps, micro vascular flaps, alloplasts like collagen membrane have also been tried in advanced cases (Arakeri and Brennan, 2013). Early intervention with habit cessation is the key to successful management in OSMF, as the disease is progressively debilitating. Pirfenidone (5-methyl-N-phenyl-2-(1H)-pyridone) is a novel anti fibrotic agent with anti inflammatory properties (Shi *et al*., 2007; Simone *et al*., 2007; Schaefer *et al*., 2011), currently used in treating idiopathic lung fibrosis (ILF) which is also an inflammatory condition mediated through transforming growth factor beta(TGF-β). Pirfenidone has been used to treat ILF successfully (Gan *et al*., 2011; Cottin, 2013).We hypothesis that Perfinidone can be a novel anti fibrotic agent (Shi *et al*., 2007) which may be beneficial in treating early stages of OSMF as both the conditions are mediated through TGF-β. We need to understand the pathogenesis of OSMF in detail both, at morphological and molecular level to consider antifibrotic drugs like Pirfenidone as a treatment modality. In chronic betel nut addicts, repeated irritation from the coarse fibres of areca nut placed in the oral cavity causes inflammation characterised by the presence of activated T cells, macrophages. Cytokines like interleukin 6, tumour necrosis factor, interferon α (Rajalalitha and Vali, 2005), connective tissue growth factor

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(CTGF) (Ekanayaka and Tilakaratne, 2013) are also synthesized. CTGF is associated with the onset and progression of fibrosis in many human tissues. Arecoline stimulated CTGF synthesis in a dose and time dependent manner in buccal mucosal fibroblasts through reactive oxygen species (ROS), NF–kappaβ pathway has been demonstrated in OSMF (Ekanayaka and Tilakaratne, 2013). The basic fibroblast growth factor (b-FGF) is another factor which interacts synergistically with other growth factors enhancing the extra cellular matrix deposition. This is upregulated in OSMF (Ekanayaka and Tilakaratne, 2013; Bishen *et al*., 2008). At molecular level, OSMF is associated with two main events namely increased collagen production and decreased degradation of collagen mediated through TGF-β (Rajalalitha and Vali, 2005; Ekanayaka and Tilakaratne, 2013). Procollagen genes are activated with elevation of procollagen proteniases levels involving procollagen C-proteinase (PCP)/bone morphogenetic protein1 (BMP1) and procollagen N-proteinase (PNP). Up-regulation of lysyl oxidase (LOX) activity is also noted leading to increased collagen production (Rajalalitha and Vali, 2005). COL1A2, COL3A1, COL6A1, COL6A3, and COL7A1 are early induced procollagen genes in fibroblasts which have been identified as TGF-β targets leading to transcriptional activation of types I and VII collagen gene expression in turn increasing collagen production (Rajalalitha and Vali, 2005; Ekanayaka and Tilakaratne, 2013). Procollagen precursors PCP/ BMP -1 and PNP are processed into collagen fibrils by procollagen proteases are induced and upregulated by TGF-β (Rajalalitha and Vali, 2005). These events lead to overproduction collagen, that are cross linked by LOX, an essential enzyme for final processing of stable, cross linked collagen fibers that are resistant to proteolysis and degradation. LOX is mediated by increased copper content of areca nut (Rajalalitha and Vali, 2005; Ekanayaka and Tilakaratne, 2013).

Tissue inhibitor of matrix metalloproteinase gene (TIMPs) and plasminogen activator inhibitor (PAI) gene are activated and upregulated in OSMF leading to collagen degradation. MMP1, MMP8 and MMP 13 are matrix metalloproteinases (MMPs) which are collagenases that degrade collagen. TIMPs inhibit the degradation of collagen by these collagenases resulting in increased collagen (Rajalalitha and Vali, 2005). Plasminogen activation system (PAS) an extracellular proteolytic system plays an important role in tissue remodelling. The active plasmin activated by PAS in turn activates pro MMPs which promotes MMPs that degrades collagen. PAS is inhibited by PAI-1 and PAI-2 genes which are activated in OSMF further preventing collagen degradation (Rajalalitha and Vali, 2005; Ekanayaka and Tilakaratne, 2013). In addition to the above mechanisms reactive oxygen species (ROS) induce oxidative stress via lipid peroxidation which contributes to malignant potential of OSMF. Increased lipid peroxidation product melonaldehyde has been demonstrated by Gupta etal in OSMF (Gupta *et al*., 2004). The above discussion deduces that collagen metabolism is primarily affected in OSMF, resulting primarily from exposure to areca nuts. An abnormal collagen deposition and decreased collagen degradation is noted, leading to an increased deposition of collagen in the oral cavity. (Rajalalitha and Vali, 2005) The integrity and repair of collagen is mediated by many growth factors, cytokines and lymphokines. TGF-β (specifically TGF-β1) has been implicated in oral fibrosis (Rajalalitha and Vali, 2005; Ekanayaka and Tilakaratne, 2013). Pirfenidone has shown to have anti-inflammatory, antioxidative stress and anti proliferative properties regulating key fibrotic cytokines and growth factors (Macias Barragan *et al*., 2010). Its pharmacological actions that can be useful in treating OSMF are enumerated below. Pirfenidone and inflammation, cytokines and growth factors. It also suppresses pro inflammatory cytokines TNF-α (Nakazato *et al*., 2002) and interleukin-6 which are upregulated in OSMF. T cell activation and proliferation is inhibited by pirfenidone in cell culture (Gan *et al*., 2011). Additionally CTGF which induces fibrosis via NF-kappaβ pathway is blocked by pirfenidone (Cho and Kopp, 2010). The basic fibroblast growth factor (b-FGF) which interacts synergistically with other growth factors enhancing the extra cellular matrix deposition in OSMF (Ekanayaka and Tilakaratne, 2013; Bishen et al., 2008) is shown to be down regulated in murine bleomycin induced pulmonary fibrosis (Gan et al., 2011).

Pirfenidone in oxidative stress

Pirfenidone is shown to ameliorate oxidative stress scavenging hydroxyl radicals in a dose-dependent manner reducing ROS (Cho and Kopp, 2010).

Perfinidone and collagen metabolism

Major connective tissue collagen is formed by type I, III, VI class of fibrillar collagen and type VII forms the anchoring fibrils. Transcriptional activation of type I and VII collagen are induced by procollagen genes COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1 which have been identified as TGF-β targets (Rajalalitha and Vali, 2005). Perfinidone decreases levels of mRNA encoding type I and III also inhibiting TGF – β1 induced collagen production from fibroblasts (Gan *et al*., 2011). TIMPs inhibits MMP which degrade the collagen matrix. TIMPs are the biologic regulators of extracellular matrix turnover. Out of the four types of TIMPs, TIMP-1 inhibits most of the MMP thereby inhibiting collagen degradation (Rajalalitha and Vali, 2005' (Ekanayaka and Tilakaratne, 2013). Perfinidone is known to down regulate TIMP-1 which is over expressed in OSMF (García et al., 2002). Plasminogen activation system plays an important role in tissue remodelling by activation of MMPs, which are regulated by PAI 1 and 2. Up regulation of PAI-1 by TGF- β has been demonstrated in OSMF (Simone *et al*., 2007; Ekanayaka and Tilakaratne, 2013) which is down regulated by perfinidone (García *et al*., 2002). Fibrosis is an effect of deregulated deposition of extracellular matrix (ECM) with progressive destruction of normal tissue (Gupta *et al*., 2004). A balance between normal collagen regulation and degradation is lost in fibrosis be it lung, cardiac, liver or oral fibrosis. Each of this fibrotic disease warrants significant research and clinical study to meet treatment protocols. Pirfenidone (5-methyl-N-phenyl-2-(1H)-pyridone) is a novel anti fibrotic agent with anti inflammatory properties (Shi *et al*., 2007; Simone *et al*., 2007; Schaefer *et al*., 2011; Macias Barragan *et al*., 2010). Any fibrotic disease is usually mediated by TGF-β and other inflammatory cytokines, with elaboration of growth factors such as b-FGF which are effectively blocked by perfinidone (Schaefer *et al*., 2011; Gan *et al*., 2011). Numerous studies in animal and humans using perfinidone have shown promising results. It has been used in mice and hamsters in effectively controlling pulmonary fibrosis, cardiac fibrosis and renal fibrosis. Pirfenidone on the other hand is not known to cause any effect on LOX that is upregulated in OSMF by the increased copper content in areca nut.

LOX leads to cross linked collagen which is difficult to degrade. Pirfenidone is an orally active molecule exhibiting a range of biological activities. It was approved in 2011 for treatment of ILF in Europe (Cottin, 2013). Initially it was developed as an anti helminthic and antipyretic agent. It is very soluble in alcohol and chloroform; in aqueous solutions, the maximum concentration is 2%. The pirfenidone molecule is able to move through cell membranes without requiring a receptor. When administered orally, it is easily absorbed in the gastrointestinal tract, reaching most tissues and crossing the blood-brain barrier (Macias Barragan *et al*., 2010).

Pharmacokinetics of pirfenidone

The drug has a t_{max} of 0.33 to 1 hour and is rapidly absorbed from oral doses with a mean t1/2 of 2 to 2.5 hours (Shi *et al*., 2007). it is metabolised in liver (Nakazato *et al*., 2002). Concomitant food intake reduces the bioavailability of the drug up to 20%. Food intake with the drug is also known to reduce the gastric irritation (Shi *et al*., 2007; Macias Barragan *et al*., 2010). The plasma pirfenidone levels fell rapidly, with a mean residence time of 6.3 min, which agrees with the rapid disappearance of the drug. Moderate extra vascular distribution occurred within 5 min with the volume of distribution at steady state (Vdss) being 0.71 ml/g, with the drug reaching the following areas in descending order: kidney, liver, ventricle, lung, spleen, pancreas, testes, GI system, brain, skeletal muscle, adrenal glands and epididymal fat pad (Macias Barragan *et al*., 2010). In any fibrotic diseases, the amount of collagen deposited in the tissue is controlled by the balance between synthesis and degradation of collagen in ECM by matrix MMPs, which are regulated by TIMPs mediated by TGF-β. This occurs at the transcriptional and translational level. TGF-β is down regulated by pirfenidone (Macias Barragan *et al*., 2010).

Safety profile of pirfenidone

Most clinical trials describe that pirfenidone is generally well tolerated in doses up to 2400 mg daily (800 mg three times daily). The most common adverse effects include gastrointestinal (nausea, dyspepsia, diarrhea, abdominal discomfort, and vomiting), anorexia, fatigue, sedation, and photosensitivity rash which are dose related (Cottin, 2013; Cho and Kopp, 2010).

Clinical trials using perfinidone

In Animal models (Table1)

Bleomycin induced lung fibrosis in mice treated with 400mg by Kakugawa *et al* in two divided doses showed decrease inflammatory and fibrotic markers and fibrosis (Schaefer *et al*., 2011). In addition to the above findings another study by Iyer *et al* showed reduction in oxidative stress in hamsters fed with 0.5% pirfenidone (Schaefer *et al*., 2011). 2400 mg of pirfenidone given in three divided doses in dogs with congestive cardiac failure for three weeks showed decrease inflammatory and fibrotic markers and fibrosis. 50% reduction of left atrial fibrosis induced by congestive cardiac failure was noted by Lee *et al* (Schaefer *et al*., 2011).

The effect of pirfenidone on unilateral urethral obstruction induced fibrosis in rats was studied. In this model, prophylactic treatment with pirfenidone (0.6–0.9% in feed) yielded a 50% reduction in unilateral urethral obstruction induced collagen deposition and also reduced expression of collagen and TGF-b mRNAs. The effect of pirfenidone in the 5/6 nephrectomy model in rats was evaluated. In this study by Shimuzu *et al*, pirfenidone treatment (0.6–0.9% in feed) prevented 60% of collagen accumulation following nephrectomy and also reduced expression of TGF-β and collagen mRNAs (Schaefer *et al*., 2011).

The efficacy of oral administration of pirfenidone at 200 mg.kg-1 in carbon tetrachloride induced hepatic fibrosis decreased liver fibrosis by 40% and significantly decreased collagen I mRNA expression as shown by Montez *et al* (Schaefer *et al*., 2011; García *et al*., 2002). The most commonly evaluated marker of fibrosis in the above studies is TGF- β. A total of 11 studies which evaluated expression of TGF- β showed that TGF- β was upregulated in the fibrotic state and that pirfenidone treatment significantly reduced TGF-β expression (Schaefer *et al*., 2011). A topical application of 10% pirfenidone solution 3 timed daily for 7 days decreased swelling and increased flexion in thermoplasty induced foreleg lameness in horses (Gan *et al*., 2011). 0.5% of 50µml pirfenidone placed in rabbits conjunctival sac showed wide distribution and fast clearance in ocular tissues. Research using this data is going on to treat glaucoma (Sun *et al*., 2011).

Table 1. Pirfenidone in animal trials

Study	Model	Condition	Dosage	Comments
Iyer et al	Hamsters	Bleomycin induced lung fibrosis	0.5% pirfenidone	decrease inflammatory and fibrotic markers and fibrosis and reduction in oxidative stress
Lee et al	dogs	fibrosis induced by congestive cardiac failure	2400 mg of pirfenidone given in three divided doses	50% reduction of left atrial fibrosis
Kakugawa et al	Mice	Bleomycin induced lung fibrosis	400mg in two divided doses	decrease inflammatory and fibrotic markers and fibrosis
Shimuzu et al	Rats	unilateral urethral obstruction induced fibrosis	prophylactic treatment with pirfenidone (0.6–0.9% in feed)	50% reduction in unilateral urethral obstruction induced collagen deposition and also reduced expression of collagen and TGF-b mRNAs
Shimuzu et al	rats	5/6 nephrectomy model	pirfenidone (0.6–0.9% in feed)	prevented 60% of collagen accumulation following nephrectomy and also reduced expression of TGF-β and collagen mRNAs
Montez et al		carbon tetrachloride induced hepatic fibrosis	oral administration of pirfenidone at 200 mg.kg-1	decreased liver fibrosis by 40% and significantly decreased collagen I mRNA expression
Giri et al	horses	thermoplasty induced foreleg lameness	10% pirfenidone solution 3 timed daily for 7 days	decreased swelling and increased flexion
Sun G et al	rabbits	conjunctival sac	0.5% of 50µml pirfenidone	wide distribution and fast clearance in ocular tissues.

Human trials (Table 2)

Clinical trials on pulmonary fibrosis associated with focal segmental glomerulosclerosis, ILF, hypertrophic cardiomyopathy, kidney disease in patients with diabetes, and fibrosis caused by radiation therapy for cancer has been done using pirfenidone (Macias Barragan *et al*., 2010).

Table 2. Pirfenidone in human trials

Study	Model	Condition	Dosage	Comments
Noble et al	Randomised, double-blind, placebo-controlled studies similarly designed Phase III trials, were conducted at 110 sites across North America, Australia and 11 European countries	patients with IPF	2403mg/day,1197mg/day or placebo in a 2:1:2 ratio and also 2403mg/day or placebo in a 1:1 ratio, administered 3 times daily with food for 72 weeks.	A 26% reduction in risk of death or disease progression was noted
Simone et al	An open label, prospective pilot study	radiation fibrosis of neck , back or extremities. The fibrosis had limited patient's movements.	used 800 mg of pirfenidone prescribed thrice daily to five patients with radiation fibrosis of neck , back or extremities for three months.	at least 25% improvement in movement following usage of pirfenidone
Shi S et al	A randomized, dose escalating study in china	48 healthy volunteers	400-600mg in fasted state	pirfinidone was well tolerated in single oral doses and no gender differences were noted for the pharmacokinetic variables
Borunda et al	pilot study	15 patients with established advanced liver disease caused by chronic hepatitis C virus infection	1200mg of pirfenidone daily for 12 months	improvement in liver necrosis, inflammation with 30% reduction of fibrosis was noted
Smith et al,.	open label pilot study	18 patients with focal segmental glomerosclerosis	800 mg of pirfenidone was administered for 5 to 37 months	A 25% improvement in glomerular filtration rate , with slowed renal function decline was observed
Armendariz-Borunda J et al	Controlled clinical trial	gel 33 patients of hypertrophic scars	8% topical 6 months	showed improvement in 66.6% patients

A multicentric, double-blind, placebo-controlled, randomised Phase III clinical trial was conducted in Japan by Azuma *et al* to determine the efficacy and safety of pirfenidone in 275 patients with IPF. Patients were randomised to pirfenidone 1800 mg per day, pirfenidone 1200 mg per day or placebo using a 2:1:2 ratios, with 267 patients evaluated for the efficacy of pirfenidone with its dose increased in a stepwise manner over four weeks. Pirfenidone was associated with a 44% reduction in the vital capacity decline compared with placebo (Cottin, 2013). Randomised, double-blind, placebo-controlled studies similarly designed Phase III trials, were conducted at 110 sites across North America, Australia and 11 European countries using pirfenidone /day, 1197mg/day or placebo in a 2:1:2 ratio and also 2403mg/day or placebo in a 1:1 ratio, administered 3 times daily with food for 72 weeks.

A 26% reduction in risk of death or disease progression was noted (Cottin, 2013). An open label, prospective pilot study by Simone *et al* used 800 mg of pirfenidone prescribed thrice daily to five patients with radiation fibrosis of neck , back or extremities for three months. The fibrosis had limited patient's movements. The study results showed at least 25% improvement in movement following usage of pirfenidone (Simone *et al*., 2007). A randomized, dose escalating study in china on 48 healthy volunteers showed that pirfinidone was well tolerated in single oral doses 400-600mg in fasted state (Shi et al., 2007) and no gender differences were noted for the pharmacokinetic variables (Shi et al., 2007)' Macias Barragan *et al*., 2010). In a pilot study by Borunda *et al*, 15 patients with established advanced liver disease caused by chronic hepatitis C virus infection were treated for 12 months using 1200mg of pirfenidone daily improvement in liver necrosis, inflammation with 30% reduction of fibrosis was noted (Macias Barragan *et al*., 2010). In an open label pilot study by Smith *et al*, 800 mg of pirfenidone was administered for 5 to 37 months in 18 patients with focal segmental glomerosclerosis. A 25% improvement in glomerular filtration rate, with slowed renal function decline was observed (Macias Barragan *et al*., 2010).

8% topical gel used in 33 patients for 6 months in treating hypertrophic scars showed improvement in 66.6% patients (Macias Barragan *et al*., 2010).

Conclusion

Clinical trials evaluating the effectiveness of pirfenidone in OSMF has not been done. It is clear that clinical trials involving this drug for fibrosis involving lung, kidney, liver and heart have shown significant improvement in ameliorating the disease intensity. Dose adjustment in OSMF patients in accordance with the clinical staging and minimal effective dosage in decreasing the existing oral fibrosis needs to be assessed. Use of topical preparations in OSMF, as the disease is localised to the oral cavity mostly has to be evaluated. Another parameter that needs to be addressed is the duration of treatment in OSMF. A positive outcome with prolonged research and numerous clinical trials, evaluating the systemic and topical uses of pirfenidone in OSMF with can give a ray of hope to these patients, helping them achieve a better quality of life.

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