International Journal of Pharma and Bio Sciences V1(2)2010

DOXYCYCLINE: AN OLD DRUG WITH A NEW ROLE IN IDIOPATHIC PULMONARY FIBROSIS

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ABSTRACT

Given the lack of knowledge of the etiology, pathogenesis and natural history of IPF, it is perhaps not surprising that that there is a lack of high quality evidence for the 'standard' treatments currently in use. In such a scenario the ideal therapy for IPF is still awaited. The present article reviews the potential role of doxycycline as a novel therapeutic option in the treatment of IPF substantiated by results of relevant studies on doxycycline. The Matrix metalloproteinases (MMP) inhibitor property of doxycycline may help it gain its role in IPF in years to come.

KEYWORDS

Doxycycline, Idiopathic Pulmonary Fibrosis, IPF, Matrix metalloproteinases (MMP) inhibitor

INTRODUCTION

Many acute and chronic lung disorders with variable degrees of pulmonary inflammation and fibrosis are collectively referred to as interstitial lung diseases (ILDs) or diffuse parenchymal lung diseases. Idiopathic pulmonary fibrosis (or cryptogenic fibrosing alveolitis) (IPF or CFA) is one of several idiopathic interstitial pneumonias. IPF is now recognized as a distinct clinical disorder.[1] Despite major accomplishments in our understanding of the pathogenesis of lung fibrosis,[2] the diagnosis and management of patients with IPF continues to pose significant challenges.[3]

The natural course of the disease is not well known. It occurs worldwide and is more common among white people, men, and people over the age of 50 years. IPF has a very poor prognosis; the median survival time following diagnosis is 3-5 years.[4]

DEFINITION[1]

IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histologic appearance of usual interstitial pneumonia (UIP) on surgical (thoracoscopic or open) lung biopsy. The etiology is unknown.

The definite diagnosis of IPF in the presence of a surgical biopsy showing UIP includes the following:

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1. Exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and collagen vascular diseases.
2. Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV1/FVC ratio) and/or impaired gas exchange [increased AaPO2, (alveolar-arterial pressure difference for 02) with rest or exercise or decreased DLco (diffusing capacity of the lung for CO)].
3. Abnormalities on conventional chest radiographs or high-resolution computed tomography (HRCT) scans.

In the absence of a surgical lung biopsy, the diagnosis of IPF remains uncertain. However, in the immunocompetent adult, the presence of all of the following major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.

Major Criteria:
- Exclusion of other known causes of ILD, such as certain drug toxicities, environmental exposures, and connective tissue diseases
- Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV1/FVC ratio) and impaired gas exchange [increased AaPO2, with rest or exercise or decreased DLco]
- Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans
- Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis

Minor Criteria:
- Age>50 yr
- Insidious onset of otherwise unexplained dyspnea on exertion
- Duration of illness ≥ 3 months
- Bibasilar, inspiratory crackles (dry or “Velcro” type in quality)

Rationale for Treatment

The rationale for the use of corticosteroids and the immunosuppressive/cytotoxic agents such as azathioprine and cyclophosphamide is based on the current hypothesis for the mechanisms underlying IPF, which is that inflammation, leads to alveolar injury, altered wound healing and fibrosis.[2]

Optimal therapy for IPF is contentious.[5] To date, most treatment strategies have been based on eliminating or suppressing the inflammatory component. No pharmacological therapy has been proven unequivocally to alter or reverse the inflammatory process of IPF. More importantly perhaps, little information has appeared supportive of the theory that the fibrotic process can be reversed.[1]

Current Therapeutic options in IPF include corticosteroids(Prednisolone), Azathioprine, N-acetylcysteine(NAC), Cyclophosphamide, Methotrexate, Chlorambucil, Pirfenidone, Endothelin-1antagonists (Bosentan), Tumour necrosis factor a (TNFa) modulator(Etanercept), Warfarin, Colchicine, Penicillamine and Cyclosporin. However none can be considered ‘‘best current treatment’’ until further data are available.[4]

Given the lack of knowledge of the aetiology, pathogenesis and natural history of IPF, it is perhaps not surprising that that there is a lack of high quality evidence for the 'standard' treatments currently in use. Controversy still exists around the currently accepted 'standard' treatment regime of corticosteroids in combination with azathioprine or cyclophosphamide (as recommended in a joint consensus statement from the ERS and the American Thoracic Society published in 2000).[4]

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In such a scenario the ideal therapy for IPF is still awaited. The present article reviews the potential role of doxycycline as a novel therapeutic option in the treatment of IPF.

METHOD

An extensive internet search was done on Pubmed, EMBASE, Google, Google Scholar and OJOSE databases. The keywords used were "doxycycline", IPF", "Idiopathic Pulmonary Fibrosis", "Pathogenesis", "Matrix Metalloproteinase Inhibitors", "TIMP", "MMP", "Case report" and "Clinical Trial". The reference section of primary studies and narrative reviews was reviewed to search for any additional primary articles that could have been overlooked by the electronic search.[6] No date or language restriction was placed on the literature search. All case reports and clinical trials in humans relevant to the subject were included in the review. The results of relevant animal experiments were also taken into consideration.

RESULTS

Animal experiments have shown that doxycycline might be useful for slowing down pulmonary fibrosis by biological activity other than antibacterial activity.[7] Inhibitory effects of doxycycline on bleomycin induced pulmonary fibrosis have been demonstrated in animal experiments.[8]

Significant improvement in different parameters has been previously reported in a case of IPF with prolonged doxycycline therapy.[9]

The results of a recent open prospective trial studying the results of long term doxycycline in IPF are encouraging. Bhattacharyya et al.[10] evaluated the effect of long term use of doxycycline in IPF patients. Patients of IPF, selected randomly from out patient services and diagnosed on the basis of HRCT(High Resolution Computed Tomography) chest, were put on doxycycline (100mg, twice a day) in an open prospective trial. They were followed up with monitoring of subjective well being along with measurement of pulse rate and arterial oxygen saturation at rest and after a fixed and certain exercise, forced vital capacity, six minutes walk test, St Georges Respiratory questionnaire, and serial chest X-rays. Out of seven patients put on doxycycline, six of them continued the drug for a mean period of 531.43 (± 328.88 days). All the patients tolerated the drug well and had shown uniform subjective and overall objective improvement in all the parameters concerned; the change in the radiological parameter being statistically significant.

DISCUSSION

The prevailing pathophysiological concept of IPF has shifted from inflammation induced fibrosis[11] to a disease of fibroblast proliferation and dysregulated fibrogenesis.[12] Abnormal lung remodeling ensues from accumulation of extra cellular matrix (ECM) following epithelial injury.[12] This is associated with a simultaneous dysregulated activity of matrix metalloproteinases (MMPs), a group of enzymes that can be related to release of fibroblast growth factor which is important for continuous stimulation of fibrogenesis in IPF.[13,14] An imbalance in matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases (TIMPs), delayed or absent reepithelialisation and increased Vascularity are noted in IPF.[13,14] Hence prevention of MMP activity could therapeutically benefit patients with IPF.

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Doxycycline, a member of the tetracycline antibiotic family is also a nonselective MMP inhibitor, with a proven safety profile.[15,16,17]

Besides doxycycline decreases monocyte chemoattractant protein – 1 (MCP-1) in human lung epithelial cells.[18] Also it has been demonstrated that monocyte chemoattractant protein-1 production by epithelial cells in IPF may be caused by the metaplastic nature of the epithelial cells and may be one of the key factors inducing the irreversible progression of IPF.[19]

MMPs inhibition and resetting the MMP-TIMP relations following epithelial injury and inhibition of MMPs is one of the recognized targets of future therapy of IPF. Doxycycline has been there in the market over 30 years, and its known property of MMPs inhibition being approved by the FDA, USA for periodontal disease.[20]

Thus there is potential role of doxycycline in IPF.

Prolonged therapy with doxycycline has been recorded to be well tolerated for over months in several conditions. In Q fever endocarditis doxycycline was given for a mean duration of 55 months (median 60 months) in combination with ofloxacin, and for a mean duration of 31 months (median, 26 months) with hydroxychloroquin, where the patients were declared cured.[21] Similar experience of Q fever endocarditis has been described in a patient with biological prosthetic aortic valve and aortic homograft; the patient was successfully treated with doxycycline and chloroquin for two years.[22] Doxycycline is licensed for up to two years or more in the treatment of acne in the same dose as is used for malaria prevention. The UK Advisory Committee for Malaria Prevention (ACMP) has concluded that there is no evidence of harm in long-term use of doxycycline and it may be taken safely for periods of at least up to two years.[23] There has been a case report of successful treatment of apparently refractory pulmonary capillary endotheliosis with doxycycline probably exploiting the same mechanism of action.[24]

CONCLUSION

Thus doxycycline, a widely used and relatively safe drug can be an effective adjunct in the treatment protocol of IPF in future. Systematically designed prospective, controlled studies have to be done to critically evaluate the potential new therapeutic aspect of doxycycline in IPF. The addition of this new drug to the list of the limited therapeutic options in IPF available currently, could be of great value in the years to come.

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