Case Report

Reactivation Pulmonary Tuberculosis in Two Patients Treated with Pirfenidone

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Abstract

We report two cases of patients with biopsy-proven idiopathic pulmonary fibrosis (IPF) who were treated with new antifibrotic agent for pirfenidone for more than 12 months. Both cases developed cavitary pulmonary tuberculosis (TB) proven by positive sputum TB culture. Both cases were treated with standard anti-TB drugs for 9 months and had complete clinical and radiological resolution. To our knowledge, these are the first reported human cases of patients with IPF who have been on pirfenidone and developed cavitary pulmonary TB.

Keywords: Idiopathic pulmonary fibrosis, pirfenidone, tuberculosis

INTRODUCTION

Pirfenidone is an orally available antifibrotic drug approved by the Food and Drug Administration (FDA) in 2014 for the treatment of idiopathic pulmonary fibrosis (IPF). It has significant antifibrotic and anti-inflammatory effects.[1]

The precise mechanism of action of pirfenidone is not fully understood but thought to inhibit transforming growth factor (TGF)-dependent collagen production, decreased fibroblastic foci, and blocking platelet-derived growth factor and decreasing fibroblast proliferation.[2]

In mice experimental model with induced chronic pulmonary tuberculosis (PTB), adding pirfenidone to slandered anti-TB regimen results in incomplete sterilization of TB. In addition, adjunctive pirfenidone treatment results in the development of persistent pulmonary cavitation, pulmonary consolidation corresponding to lobar pneumonia early in the course of disease, and induce drug resistance in this mice experimental model.[3] These observations strongly suggest that pirfenidone affects host control of TB infection through marked increase in matrix metalloproteinase.[3]

The incidence and mortality of PTB are high among patient with IPF.[4,5] Multiple conducted clinical trials of pirfenidone did not report an increase in either incidence or reactivation of TB; however, these trials were conducted in low TB prevalence regions. We report PTB reactivation in two IPF patients treated with pirfenidone.

CASE REPORTS

Case 1

A 64-year-old woman originally presented with cough and shortness of breath in February 2015. Her subsequent investigations with computed tomography (CT) chest and video-assisted thoracoscopic surgical (VATS) confirmed usual interstitial pneumonia-IPF (UIP/IPF). She was discussed in our interstitial lung disease (ILD) multidisciplinary meeting, and consensuses were to start her on pirfenidone according to her weight. She was put on 1800 mg in three divided doses in March 2015 and had regular follow-up in our ILD clinic. Twelve months after the initiation of pirfenidone, she presented with cough, fever, and weight loss to our emergency room. The chest X-ray and CT scan of her chest have shown a large cavitary lesion in the right upper lobe [Figure 1a]. Subsequent workup with bronchoscopy and bronchoalveolar lavage has confirmed smear- and polymerase chain

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reaction (PCR)-positive TB. Subsequently, the mycobacterium TB (MTB) was shown to be pansensitive to first-line anti-TB treatment. Her HIV status was shown to be negative. The patient received 9 months of standard treatment with four drugs initiation and two drugs continuation for subsequent 7 months. She made a full recovery follow-up CT showing significant improvement [Figure 1b].

**Case 2**

A 58-year-old man was diagnosed with UIP/IPF based on clinic radiological and VATS biopsy in 2014. He opted for treatment with pirfenidone and started at 2400 per day in divided doses since January 2015. After he has been on pirfenidone for 20 months, he presented with cough and his CT scan in follow-up clinic [Figure 2a] showed a large cavitating lesion in the left upper lobe. The sputum induction in this case has shown smear- and PCR-positive TB that was subsequently confirmed to be pansensitive MTB. He received 7 months of treatment with standard anti-TB and had resolution of his CT changes [Figure 2b] and clinical improvement. His HIV status was negative.

**DISCUSSION**

Pirfenidone is an oral antifibrotic agent that was approved by FDA in 2014 for the treatment of IPF. The drug is shown to have antifibrotic and anti-inflammatory properties in multiple phase 3 clinical trials that resulted in preserving the lung functions and hence slow down disease progression.[7] The precise mechanism of action of pirfenidone is not fully understood but thought to inhibit TGF-beta1-dependent collagen production, decreased fibroblastic foci, and blocking platelet-derived growth factor.[2]

Patients with IPF are known to have high incidence of PTB.[1] PTB is known to causes lung injury, fibrosis, and cavitations. The TB granuloma is known to harbor tuberculous bacilli for decades without causing active disease, depending on tuberculous bacilli pathogenicity and host factors; future reactivation leads to causation, cavitations, and TB activation.[8]

There are research studies in animal models that have proven that pirfenidone promotes pulmonary caviation and drug resistance in mouse models with TB.[3] Furthermore, pirfenidone has immune-modulating activities, by altering T-cell proliferation and cytokine release in response to T-cell receptor.[9] We believe to our knowledge no human cases are reported to develop cavitary TB while on pirfenidone at the same time. Our two cases were diagnosed IPF based on clinic, radiological, and histological data. The decision was taken to start them on pirfenidone standard dose, and they were clinically followed up. There was no account of past PTB or any exposure to any other immunosuppressive treatment in the interim period. The workup before the start of pirfenidone cases has not led to any suspicion of underlying PTB infection. Both cases suffered from pansensitive MTB and responded well to anti-TB treatment. Most of the clinical trial done on pirfenidone was in low incidence countries for TB. The reported annual TB incidence rate of 18/100,000 population in Saudi Arabia therefore considered in the medium-risk countries for TB.[10] These cases would imply that pirfenidone has probably led to reactivation of probable latent TB. Although we are not certain that pirfenidone is the cause of TB reactivation, it certainly may contribute to TB reactivation. This is needed to be confirmed by doing a prospective study. However, it will be strongly advised to carefully watch patient for developing any features of TB infection when commenced on antifibrotic, especially pirfenidone in medium to high TB burden countries, especially with the increase incidence of IPF and wider use of treatment with antifibrotics specially pirfenidone.

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**Conflicts of interest**

There are no conflicts of interest.

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