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Clinical Trial Paper

Azathioprine response in patients with fibrotic connective tissue disease-associated interstitial lung disease

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ABSTRACT

Background: Azathioprine is a commonly prescribed therapy for connective tissue disease-associated interstitial lung disease (CTD-ILD). Combination therapy that included azathioprine was recently shown to increase the risk of death and hospitalization in patients with idiopathic pulmonary fibrosis. Whether azathioprine increases the risk of adverse outcomes in patients with fibrotic CTD-ILD, including those with CTD-associated usual interstitial pneumonia (UIP), remains unknown.
Methods: A retrospective cohort analysis was performed to determine the combined incidence rate of death, transplant and respiratory hospitalization associated with azathioprine exposure. A fibrotic CTD-ILD cohort treated with mycophenolate mofetil served as a comparator group. Incidence rates were compared with an incidence rate ratio (IRR) generated by negative binomial regression. Longitudinal pulmonary function response was then assessed using mixed effects linear regression models.
Results: Fifty-four patients were treated with azathioprine and forty-three with mycophenolate. Medication discontinuation due to non-respiratory side effects occurred in 27% and 5% of the azathioprine and mycophenolate cohorts, respectively. The combined incidence rate of adverse outcomes was 0.015 and 0.013 for azathioprine and mycophenolate, respectively (IRR 1.23; 95% CI 0.49–3.12; $p = 0.66$). Similar incidence rates were observed among those with CTD-UIP (IRR 0.83; 95% CI 0.21–3.31; $p = 0.79$). Both groups demonstrated pulmonary function stability over time, with the azathioprine group demonstrating a marginal improvement.
Conclusions: A significant minority of patients could not tolerate azathioprine due to non-respiratory side effects. Of those who did tolerate azathioprine, a similar incidence of adverse outcomes was observed as those treated with mycophenolate. Both therapies were associated with stability in pulmonary function.

1. Introduction

Interstitial lung disease (ILD) is a common manifestation of connective tissue disease (CTD) and may lead to significant morbidity and mortality [1,2]. The CTDs complicated by ILD include systemic sclerosis, rheumatoid arthritis, polymyositis and dermatomyositis, Sjogren's syndrome, mixed connective tissue disease and systemic lupus erythematosus [3]. CTD-associated ILD is most commonly associated with a pattern of non-specific interstitial pneumonia (NSIP) on high-resolution computed tomography (HRCT) and/or surgical lung biopsy (SLB), followed by usual interstitial pneumonia (UIP) [4,5]. While survival among patients with CTD-associated ILD is generally favorable when compared to patients with idiopathic pulmonary fibrosis (IPF), this survival benefit is less pronounced in the setting of UIP and is likely influenced by CTD etiology [5–8].

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Treatment of CTD-associated ILD generally targets the immune system, which is responsible for the production of autoantibodies that characterize specific CTDs. In addition to corticosteroids, common first-line therapies include azathioprine and mycophenolate mofetil, both of which act to inhibit B and T-lymphocyte proliferation [9,10]. Data regarding the use of these therapies to treat CTD-associated ILD is sparse and largely confined to case series and a small uncontrolled clinical trial [11–17]. A recent randomized controlled trial conducted in patients with IPF showed that azathioprine, when used in combination with prednisone and *N*-acetylcysteine, significantly increased the risk of death, hospitalization and IPF exacerbation. It is unknown whether the use of azathioprine in patients with fibrotic CTD-associated ILD, including those with UIP, increases the risk of adverse outcomes in this patient population.

In this investigation we conducted a single-center retrospective longitudinal analysis of patients with fibrotic CTD-associated ILD to determine whether treatment with azathioprine was associated with an increased incidence of adverse outcomes, including death, lung transplantation and respiratory hospitalization. Patients receiving mycophenolate mofetil were used as a control group, as this therapy has been previously shown to be safe and well-tolerated in patients with CTD-associated ILD [13,14]. We then performed a longitudinal analysis of pulmonary function to determine the change in percent predicted forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) associated with azathioprine and mycophenolate mofetil therapy over time.

2. Methods

2.1. Study design

This investigation was conducted at the University of Chicago and was approved by our Institutional Review Board (IRB protocol #14163-A). The University of Chicago ILD registry was used to identify patients followed from 2006 to 2015 with a diagnosis of CTD-associated ILD. HRCTs were reviewed by two chest radiologists (JC and SM) to identify patients with fibrotic ILD, defined as the presence of reticulation with traction bronchiectasis, traction bronchiolectasis, or subpleural honeycombing. The electronic medical record was reviewed to identify patients in this cohort treated with azathioprine or mycophenolate mofetil. Other pertinent data extracted from the electronic medical record included demographic information (age, race/ethnicity, gender), tobacco use, medications including systemic corticosteroids and other disease modifying anti-rheumatic drugs (DMARD), including tacrolimus, biologics/tumor necrosis factor-alpha inhibitors, IV immunoglobulin, rituximab, cyclophosphamide, methotrexate, penicillamine, hydroxychloroquine, physical examination findings including clubbing and crackles, laboratory studies including complete blood count and liver function testing (LFT), diagnostic studies (HRCT and SLB) and pulmonary function testing (PFT) including percent predicted FVC, and percent predicted DLCO.

The first period of treatment with either azathioprine or mycophenolate mofetil after establishing care at our institution was used to conduct this analysis. Crossing over from one therapy to another was allowed if it occurred within 4 weeks of therapy initiation and was due to a non-respiratory side effect. One patient was excluded due to receiving both therapies concurrently. Adverse events were defined as death, lung transplantation and respiratory hospitalization. The electronic medical record, social security death index and telephone communication with patients and family members were used to ascertain adverse events. Follow-up time was censored on Dec 1, 2015. Patients with at least 2 PFTs >90 days apart were included in the longitudinal PFT analysis.

2.2. Statistical analysis

Continuous variables were reported as means with standard deviation (SD) or medians with interquartile range and were compared using a two-tailed student's t-test or Wilcoxon rank sum test, as appropriate. Categorical variables were reported as counts and percentages and compared using the Chi-square test or Fisher's exact test, as appropriate. Adverse outcomes, including death, transplant and respiratory hospitalization were treated as count data with multiple events possible for a given patient. A combined endpoint incidence rate was determined for each treatment group and incidence rate ratio (IRR) determined using negative binomial regression.

Longitudinal analysis of pulmonary function change associated with azathioprine and mycophenolate mofetil therapy was conducted using mixed-effects regression models. Based on exploratory analysis with restricted maximum likelihood modeling, an exchangeable variance-covariance-correlation structure was chosen for FVC modeling while an autoregressive structure was chosen for DLCO modeling. PFTs were grouped into 1-year intervals to allow for time course alignment. Missing observations for DLCO were imputed to the lowest quartile mean of 25% to account for individuals unable to perform this procedure. Longitudinal data are presented graphically using locally weighted scatterplot smoothing. Summary statistics with $p < 0.05$ were considered to be statistically significant. All statistical analyses were performed using Stata (StataCorp. 2013. Release 13. College Station, TX).

3. Results

Of 1205 patients screened, 209 carried a diagnosis of CTD-ILD, including 182 with evidence of pulmonary fibrosis on HRCT (Fig. 1). Of those with fibrotic CTD-associated ILD, 64 were initially treated with azathioprine and 33 with mycophenolate mofetil. Ten patients (16%) initially treated with azathioprine experienced non-respiratory side effects and were subsequently transitioned to

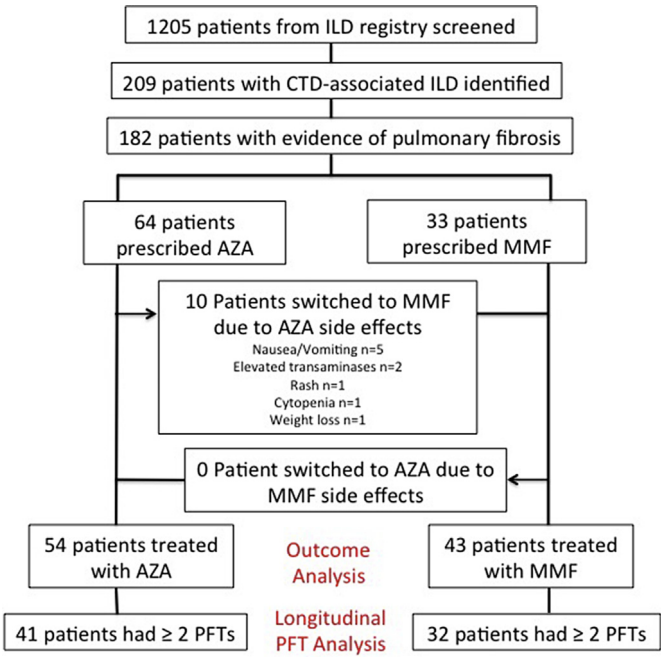

Fig. 1. Consort diagram.