Azathioprine in Connective Tissue Disease-Associated Interstitial Lung Diseases. How Valuable?

Aldehaim AY1*, AboAbat A2, and Alshabanat A1,3
1Department of Medicine, King Saud University, Riyadh, Saudi Arabia
2Department of Medicine, University of Toronto, Toronto, Canada
3Department of Medicine, McMaster University, Hamilton, Canada

Abstract

Objective: To systematically review the use of azathioprine as a treatment for connective tissue disease-associated interstitial lung disease (CTD-ILD) in terms of effectiveness and safety.

Materials and methods: A literature search was performed using the PubMed, EMBASE, CINAHL, Cochrane, and Scopus databases. The search was restricted to articles published in English from 1950 to March 2018 that examined the use of azathioprine in patients with CTD-ILD and determined its effects on a primary or secondary endpoint. This review included studies that measured the impacts of azathioprine in terms of effectiveness and safety.

Results: The search identified 15 studies with a total of 424 subjects. Two hundred twenty patients received azathioprine. A majority of the studies failed to provide clear evidence for the effectiveness of azathioprine. The reported adverse events were: death 4.5% (n=10), infection 1.3% (n=3), myelosuppression 0.9% (n=2), and malignancy 0.45% (n=1). The rate of azathioprine discontinuation due to treatment failure was 2.7% (n=6). Conclusions: No clear impacts of azathioprine have been reported, yet this review reveals that the drug is less useful than previously believed. In contrast to our current knowledge, this review suggests that the ILD histopathological pattern appears to be the most important determinant of treatment responses and prognosis, and treatment decisions should be based on this parameter, rather than the background CTD. AZA is a relatively safe option. More well-designed studies are needed. The recruitment of subjects based on the ILD pattern rather than CTD may produce more consistent results.

Keywords: Connective tissue disease; Interstitial lung disease; Azathioprine; Effectiveness; Safety

Abbreviations: CTD: Connective Tissue Disease; ILD: Idiopathic Interstitial Pneumonia; CTD/ILD: Connective Tissue Disease-Associated Interstitial Lung Disease; NOS: Modified Newcastle-Ottawa Scale; PFT: Pulmonary Function Test; FVC: Forced Vital Capacity; VC: Vital Capacity; TLC: Total Lung Capacity; DLCO: Diffusion Capacity for Carbon Monoxide; HRCT: High Resolution CT Scan; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; SSC: Systemic Sclerosis; SSJ: Sjogren Syndrome; MCTD: Mixed Connective Tissue Disease; PM: Polymyositis; DM: Dermatomyositis; UIP: Usual Interstitial Pneumonia; AIP: Acute Interstitial Pneumonia; NSIP: Nonspecific Interstitial Pneumonia; COP: Cryptogenic Organizing Pneumonia; OP: Organizing Pneumonia; AZA: Azathioprine; MMF: Mycophenolate Mofetil; CYC: Cyclophosphamide; FAST: Fibrosing Alveolitis Scleroderma Trial; SLS: Scleroderma Lung Study; RCT: Randomized Clinical Trial; Mg: Milligram; Mg/d: Milligram/day.

Background

Connective tissue diseases (CTDs) are a group of autoimmune inflammatory disorders, that target different body systems to various extents. The respiratory system is one of the most common systems implicated in various CTDs. The entire respiratory tract, including the lungs, pleura, airways, pulmonary vessels, and respiratory muscles, can be involved [1]. CTDs have a myriad of clinical and radiological manifestations, from acutely inflammatory to progressively chronic and fibrotic [2]. Compared to interstitial lung diseases (ILD) without an underlying CTD, connective tissue disease-associated interstitial lung disease (CTD-ILD) share similar clinical, pathological, and radiological forms, yet differ tremendously in terms of treatment and prognosis. Several pharmacological agents, most commonly azathioprine (AZA), cyclophosphamide (CYC), and mycophenolate mofetil (MMF), have been used to treat these conditions. The latter has been increasingly recognized as the standard immunomodulator for CTD-ILD treatment. The objective of this study is to scrutinize the evidence for AZA use in this population in terms of effectiveness and safety. AZA is a purine analog that is commonly used in combination with corticosteroids to manage various forms of CTD-ILD. However, little data is available to support its use. Similar to other agents, its use is mainly derived from studies conducted on patients with ILDs without an underlying CTD [3].

Materials and Methods

Search strategy

A literature search was conducted of the PubMed, EMBASE, CINAHL, Cochrane, and Scopus databases for all English language articles published from 1950 to March 2018 that investigated the use of AZA in patients with CTD-ILD and determined its effects on. Searches were conducted utilizing MeSH, with the following keywords: RA, Rheumatoid Arthritis, SLE, Systemic Lupus Erythematosus, Myositis, Polymyositis, Dermatomyositis, Scleroderma, Systemic Sclerosis, SSC, Mixed Connective Tissue Disease, MCTD, Sjogren’s, SJ, Remission, Relapse, Induction, and Maintenance. Additionally, two searches were conducted using the keywords interstitial lung disease or ILD or Pneumonitis or Pulmonary Fibrosis or Alveolitis or Azathioprine or Imuran, and then cross-matched using “AND”. The result was again cross-matched with the first search using “AND” to obtain studies that...
described the use of AZA in CTD-ILD. Nine reviews were meticulously searched, looking for any missing information [2-10]. The initial search yielded 633 manuscripts. After screening the abstracts and removing duplicates, 55 full-text articles were assessed for eligibility. The search process is illustrated in Figure 1. Patients with CTDs without an established ILD diagnosis, those with overlap-syndromes, or post-bone marrow transplant patients were excluded.

**Study selection and data extraction**

Based on prior decision, studies were not pooled due to data heterogeneity. Two reviewers (AD and AA) independently reviewed the search strategies and results and examined the reference lists of the studies to identify any other pertinent reports. The following information was extracted from eligible studies: design, sample size, eligibility criteria, intervention, outcome, and safety results. We used the Modified Newcastle-Ottawa Scale (NOS) [11] to assess the quality of the included studies. All studies, except RCTs and case-reports, were independently assessed by two reviewers (AD and AS). Any differences were resolved by consensus. Studies fulfilling five or more of the nine criteria were considered to be of moderately high quality.

**Outcome endpoints**

Effectiveness outcomes comprises pulmonary function test (PFT) components, including the forced vital capacity (FVC), diffusing capacity of carbon monoxide (DLCO), vital capacity (VC), and total lung capacity (TLC); changes in high-resolution CT scans (HRCT); quality of life measures; and rate of discontinuation due to treatment failure. Safety outcomes included the rates of myelosuppression, infection, malignancy, and death.

**Results**

Among the identified studies, 15 were included. Overall, 424 subjects were included; 220 of whom received AZA. These studies are described in Table 1. All of studies were of acceptable quality, with the exception of the study by Dheda et al. [12]. Studies had a median quality score of 7/9. The quality assessment process is summarized in Tables 2 and 3.

**Description of the included studies**

**Rheumatoid arthritis (RA):** Cohen et al. [13] reported a case study of a patient with RA and usual interstitial pneumonia (UIP) who showed a progressive improvement after treatment with AZA for over 5 years, allowing prednisone tapering (10 mg/d). Conversely, in a case report of AZA toxicity by Ishida et al. [14], AZA was associated with clinical and radiological deterioration in a patient with both RA and fibrotic-nonspecific interstitial pneumonia (NSIP). These findings were confirmed later upon the re-introduction of AZA. A remarkable improvement was noted after AZA discontinuation and the administration of 20 mg of prednisolone.

**Systemic lupus erythematosus (SLE):** In the study by Matthay et al. [15], AZA was administered to seven of 12 patients with SLE complicated by acute lupus pneumonitis (ALP), due to a failure to respond to corticosteroids. Similar improvements in clinically relevant PFT parameters were observed in patients who received the combination therapy (1 improved+ 2 stabilized) compared with steroids alone (2 improved+1 stabilized), with a slight advantage in the latter group in terms of number of deaths (two vs. four). The follow-up duration ranged from 14–48 months. Peter et al. [16] reported findings...
In a 47 years old female with RA-UIP, VC at baseline: 960 ml (30% of predicted) - 5 years on maintenance: 1675 ml (56% of predicted).

In a patient with RA-NSIP presenting with fibrotic changes, AZA was administered after the addition of AZA, the condition improved after removal. Similar changes were noted again after reintroducing AZA 43 days later.

A 47 year old male with SLE and fibrosing alveolitis (on 7.5 mg of prednisolone /d) - started on 125 mg of AZA/d in addition to steroids. It was discontinued after 6 days because of deterioration, but changes were noted again after reintroducing AZA 43 days later.

All subjects received steroids. AZA was a steroid-sparing agent concomitantly.

-Effects of medications were assessed at 6 and 12 months.
-Overall HRCT resolution: ILD improvement: 1 received steroids + AZA, 39 (85%) of patients were steroid resistant, of whom 10 patients were treated subject experienced Grade 1 medication toxicity (invasive pulmonary aspergillosis).
-ILD deterioration: 1 received AZA alone or combination with Rituxab (n=1)

Reevaluation after a period of 6-12 months:
-10 (23%) AZA-4 (44%) MMF-, and -3 (23%) AZA-4 (44%) MMF-, and -3 (23%) AZA-4 (44%) MMF-, and -3 (23%) AZA-4 (44%) MMF-, and -3 (23%) AZA-4 (44%) MMF-, and -3 (23%) AZA-4 (44%) MMF-, and

4 patients died (on AZA + Prednisone): 2 from respiratory failure, 1 from a concomitant Nocardia infection, and 1 from a central nervous system vascular thrombosis.
### FVC and dyspnea score Measures were assessed at baseline, 12 months, and 18 months. The baseline FVC (%) was 4.25 ± 3.53 (n=21 patients), increased to 63.38±6.15 after 12 months (p<0.01). The mean-difference change in FVC between baseline and post-treatment in the AZA group was +15.0 ± 14.5, p=0.01. At 12 months, no side effects were reported in the AZA group, however, in the CYCtreated group, two patients presented leucopenia that required a temporary dose reduction.

3 patients suffered side effects attributed to AZA use: 1 case of pulmonary tuberculosis (6 months), and 1 case of ERT (18 months). One patient died an unknown cause at 18 months, while 2 patients maintained the AZA dose. The baseline FVC was 4.25 ± 3.53 (n=21 patients), increased to 63.38±6.15 after 12 months (p<0.01). The mean-difference change in FVC between baseline and post-treatment in the AZA group was +15.0 ± 14.5, p=0.01. At 12 months, no side effects were reported in the AZA group, however, in the CYCtreated group, two patients presented leucopenia that required a temporary dose reduction.

### Table 1: Summary of data from selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Characteristics</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhedia, et al. [12]</td>
<td>Patients with SSC and showing progression of ILD</td>
<td>-6 monthly pulses of 0.6 mg/m2 CYC followed by oral AZA for 18 months</td>
<td>-8 patients received AZA; 7 showed stabilization after CYC treatment, 1 worsened, 1 died (30%)</td>
</tr>
<tr>
<td>Bencosme, et al. [21]</td>
<td>Patients with SSC and IFI</td>
<td>-6 monthly pulses of 0.6 mg/m2 CYC followed by oral AZA for 18 months</td>
<td>-8 patients received AZA; 7 showed stabilization after CYC treatment, 1 worsened, 1 died (30%)</td>
</tr>
<tr>
<td>Poomphong, et al. [22]</td>
<td>Patients with SSC and with overlap of rheumatic disease</td>
<td>-6 monthly pulses of 0.6 mg/m2 CYC followed by oral AZA for 18 months</td>
<td>-8 patients received AZA; 7 showed stabilization after CYC treatment, 1 worsened, 1 died (30%)</td>
</tr>
<tr>
<td>Ludici, et al. [23]</td>
<td>Patients with SSC and showing progression of ILD</td>
<td>-6 monthly pulses of 0.6 mg/m2 CYC followed by oral AZA for 18 months</td>
<td>-8 patients received AZA; 7 showed stabilization after CYC treatment, 1 worsened, 1 died (30%)</td>
</tr>
</tbody>
</table>

### Table 2: Summary of data from selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Characteristics</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhedia, et al. [12]</td>
<td>Patients with SSC and showing progression of ILD</td>
<td>-6 monthly pulses of 0.6 mg/m2 CYC followed by oral AZA for 18 months</td>
<td>-8 patients received AZA; 7 showed stabilization after CYC treatment, 1 worsened, 1 died (30%)</td>
</tr>
<tr>
<td>Bencosme, et al. [21]</td>
<td>Patients with SSC and IFI</td>
<td>-6 monthly pulses of 0.6 mg/m2 CYC followed by oral AZA for 18 months</td>
<td>-8 patients received AZA; 7 showed stabilization after CYC treatment, 1 worsened, 1 died (30%)</td>
</tr>
<tr>
<td>Poomphong, et al. [22]</td>
<td>Patients with SSC and with overlap of rheumatic disease</td>
<td>-6 monthly pulses of 0.6 mg/m2 CYC followed by oral AZA for 18 months</td>
<td>-8 patients received AZA; 7 showed stabilization after CYC treatment, 1 worsened, 1 died (30%)</td>
</tr>
<tr>
<td>Ludici, et al. [23]</td>
<td>Patients with SSC and showing progression of ILD</td>
<td>-6 monthly pulses of 0.6 mg/m2 CYC followed by oral AZA for 18 months</td>
<td>-8 patients received AZA; 7 showed stabilization after CYC treatment, 1 worsened, 1 died (30%)</td>
</tr>
</tbody>
</table>
FAST Systemic Sclerosis

RCT

45
-17 withdrew
-22 allocated to active treatment
-23 allocated to receive placebos

Inclusion criteria:
- Patients who were 18-75 years old with lung fibrosis diagnosed by HRCT or biopsy.
- Exclusion criteria:
  - A history of treatment with AZA, CYC, or a high dose of steroids for more than 3 months;
  - Severe systemic or psychological disease;
  - Pregnancy;
  - Drug abuse

Subjects were allocated to receive low-dose prednisolone and 6 infusions (monthly) of CYC followed by oral AZA or placebo Primary endpoints: FVC and DLCO Secondary endpoints: HRCT and dyspnea scores

FVC, DLCO, HRCT, and dyspnea scores
- The trial did not reveal a significant improvement in the primary or secondary endpoints in the active treatment group compared with the group receiving the placebo
- Estimates of the relative treatment effect adjusted for baseline FVC revealed a favorable outcome for FVC of 4.19% [95% CI] -0.57-8.95; p = 0.08

After allocation, 7 patients withdrew: 3 experienced a decrease in lung function, 2 experienced side effects, 1 had poor IV access, and 1 was diagnosed with a malignancy
- After 1 year, 1 subject receiving AZA presented an abnormal liver function test requiring withdrawal

Suto, et al. [26]

Systemic Sclerosis

Case Report

1

A patient with SSC complicated with interstitial pneumonia received AZA

- Developed pure red cell aplasia 1 year after usage

Oldham, et al. [25]

All

Retro-spective Cohort

97

Patients with connective tissue disease (ILD, and UIP)

-64 received AZA
-33 received MMF

At the beginning of the trial: 10 subjects switched to MMF due to nonrespiratory effects of AZA. Study duration: from 2006 to 2015

FVC and DLCO Both groups exhibited a stabilization of pulmonary function over time, with the azathioprine group displaying a marginal improvement.

At follow up: the medication was discontinued by 7 patients in the AZA group and 2 patients in the MMF group.
In the AZA group, 3 patients died, 2 underwent transplants, and 17 required respiratory hospitalization; meanwhile, 1 death, 1 respiratory hospitalization, and 1 transplant occurred in the MMF group.

Table 1: Characteristics of the included Studies.
from a patient with SLE complicated with fibrosing alveolitis and arthritis who had initially been treated with 7.5 mg of prednisolone (for the last 18 months) with a partial response. Later, the patient presented with cyanosis with severe dyspnea; the prednisolone dose was increased to 60 mg. Ten days later, the dosage was reduced to 20 mg, resulting in persistent exertional dyspnea. A 125 mg AZA treatment was added at this point. Six months later, the PFT improved, cyanosis had disappeared, and only mild dyspnea was observed, allowing the tapering of AZA to 100 mg and prednisolone to 6 mg.

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total score</th>
<th>Overall comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mira-Avendano et al. [17]</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>7/9</td>
<td>Somewhat representative, 14.3% males and 85.7% females</td>
</tr>
<tr>
<td>Marie et al. [18]</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>Roca et al. [20]</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>Deheinzelin et al. [19]</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>Dheda et al. [12]</td>
<td>*</td>
<td>**</td>
<td></td>
<td>3/9</td>
<td>not truly representative of target population, all females, non-smokers; 27% lost to follow up</td>
</tr>
<tr>
<td>Berezne et al. [21]</td>
<td>***</td>
<td>*</td>
<td>***</td>
<td>7/9</td>
<td>somewhat representative, 74% were females</td>
</tr>
<tr>
<td>Poormoghim et al. [22]</td>
<td>***</td>
<td>**</td>
<td>***</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>Ludici et al. [23]</td>
<td>***</td>
<td>**</td>
<td>***</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>Oldham et al. [25]</td>
<td>***</td>
<td>**</td>
<td></td>
<td>7/9</td>
<td>28% of patients discontinued therapy in both groups, mainly due to side effects</td>
</tr>
</tbody>
</table>

Table 3: Quality assessment.
Inflammatory myopathies

Adevano et al. [17] retrospectively analyzed 46 patients with steroid-resistant polymyositis (PM)/dermatomyositis (DM)-associated ILD who were treated with immunosuppressants. Twenty-four patients received CYC, 13 received AZA, and twenty-four received MMF. FVC, DLCO, dyspnea, prednisone dose, and tolerance were assessed at six and 12 months. The results revealed a substantial improvement in dyspnea, a reduction in steroid use, and PFT stabilization. No significant differences were observed between the three groups. Radiological patterns on HRCT were included organizing pneumonia (OP) in 17 patients (37%), NSIP in 16 patients (35%), UIP in nine patients (19%) and a mixed pattern in four patients (9%). A cohort of 66 patients with anti-Synthetase syndrome was examined by Maire et al. [18], 27 received AZA. A significant improvement/stabilization was observed for the different agents as follows: MMF (83%), CYC (72%), and AZA (58%). ILD included OP (n=11), NSIP (n=9), and UIP (n=16). The presence of the UIP pattern, low baseline DLCO, and age >55 years were more prominent factors in the deteriorated group.

Sjogren’s syndrome (SSJ): In a study by Deheinzelln et al. [19], 11 of 19 patients were treated with AZA + prednisolone (1 mg/kg initially, subsequently tapered to 10 mg/day). At six months, five subjects had dropped out of the series, and four received a steroid alone. At 12 months, the AZA treatment increased the FVC in seven patients, stabilized the FVC in three patients, and worsened the FVC in one patient; one of the patients who received the steroid alone exhibited an improvement, and four stabilized. Roca et al. [20] studied subjects with various ILD patterns, including NSIP (n=7), UIP (n=5), OP (n=2), and lymphocytic interstitial pneumonia (n=2). Two subjects received steroids +AZA: one stabilized and one deteriorated. Another two subjects received AZA +steroids + concomitant agents: one improved and one stabilized. The median follow-up was 24 months. This study noted a favorable response to steroids in patients with all ILD patterns, compared to patients presenting the UIP pattern.

Systemic Sclerosis (SSC): In the case series reported Dheda et al. [12] of 11 subjects with SSC-ILD, 8 subjects received AZA + low-dose prednisone for at least 12 months. Three subjects stopped taking AZA at 2-6 months, due to side effects related to AZA. The results showed improved FVC (%) from 54.25 ± 3.53 at baseline to 63.38±6.15 after 12 months and an improved mean dyspnea score from 1.55 ± 0.19 at baseline to 0.50 ± 0.19 at 12 months. However, the results were not statistically significant. Berezne et al. [21] conducted a retrospective open label study including 27 subjects with SSC-ILD who initially received monthly CYC pulses for 6 months. Eighteen subjects (70%) who stabilized/improved after CYC induction therapy subsequently received AZA, while those whose condition worsened (30%) after CYC induction therapy received MMF. In the AZA group, FVC, and TLC parameters were 70% and 51% at six and 24 months, respectively. Meanwhile, both parameters continued to worsen in the MMF group. Poormoghim et al. [22] examined 2 cohorts of subjects with SSC-ILD who were assigned to receive AZA (15 subjects) or CYC (21 subjects). Both groups received an additional low dose of prednisolone (≤10 mg) for 6 months. Statistically significant differences in pre/posttest scores were observed for the AZA-treated group compared with the CYC-treated group. Remarkably, the CYC-treated group had a shorter disease duration and more diffuse SSC. In the study by Ludici et al. [23], similar to the protocol used by Berezne et al., CYC responders received AZA and the majority continued to exhibit a stable response, while nonresponders received MMF and continued to deteriorate. Only one PFT reading was measured after the addition of a maintenance agent, with a median follow-up of 36 months. In the

Safety

Oldham et al. [25] assessed adverse outcomes of AZA compared to MMF in a retrospective study of patients with fibrotic CTD-ILD with follow-up over four years. Fifty-four and 43 patients were treated with AZA and MMF, respectively. After adjusting for major factors, therapy was discontinued by 28% of patients in both groups; both groups exhibited a stable PFT, with a marginal improvement in the AZA group. Reasons for discontinuation in the AZA-treated group were mainly side effects in 13% and disease progression/treatment failure in 10%. Similar outcomes were observed in the MMF-treated group. Suto et al. [26] reported a case of a patient with SSC-ILD who developed pure red cell aplasia after starting AZA.

The disease duration (6-48 months) and AZA doses (1-3 mg/kg/d) varied substantially among the studies included in this review. AZA was mainly administered as a maintenance agent, but was administered as an induction agent in six studies. The reported adverse events were: death 4.5% (n=10), infection 1.3% (n=3), myelosuppression 0.9% (n=2), and malignancy 0.45% (n=1). The rate of AZA discontinuation due to treatment failure was 2.7% (n=6). Safety results are summarized in Figure 2.

Discussion

ILD in the context of CTD poses a greater burden that perhaps has been underestimated in the past few decades. Little data is available from prospective studies, and the optimal treatment remains unknown. In patients with RA, the most observed pattern is UIP [27]. Cohen et al. reported a case study of a patient who achieved an excellent response to AZA with steroid tapering. Improvement was noted one week after the addition of AZA. Thus, the effect of AZA is uncertain, as the onset of action is delayed (four-twelve weeks). The possibilities of spontaneous remission or an effect of the steroid alone cannot be excluded. Ishida et al. confirmed a case of AZA-induced worsening of ILD in a patient with RA complicated with fibrotic-NSIP after the reappearance of
consolidations and ground-glass opacities, which differed from the baseline imaging. A dramatic improvement was observed after the discontinuation of AZA and steroid administration; this adverse event is rare and is more frequently described in the postrenal transplant population [28].

In patients with SLE, the prevalence of ILD has been estimated to be 3-9% [29], mostly in chronic forms. A distinct acute form observed in patients with SLE is ALP. Matthey et al. failed to show benefits of AZA when added to prednisone. Only one patient showed improvement in a period of less than four weeks after AZA introduction, and thus the role of AZA remains uncertain. Interestingly, the clinical presentation, imaging, and histopathological findings are almost identical to idiopathic acute interstitial pneumonia (Hamman-Rich syndrome); only the nomenclature differs in the setting of SLE [16]. In the case study reported by Peter et al., the progression of ILD was halted by AZA and PFT improved. The patient was diagnosed with fibrosing alveolitis (historically synonymous with UIP/IPF) based on a chest X-ray alone, which is not sufficient for an accurate ILD diagnosis. With the rapid tapering of steroid initially and similar baseline steroid requirement, the AZA impact may have been overestimated.

In patients with inflammatory myopathies, the ILD occurrence is higher than in other CTD cohorts [30,31]. Adevano et al. did not observe a statistically significant improvement between the agent of choice; all were viable alternatives. The results revealed a substantial improvement in the MMRC grade at six and 12 months, while the PFT remained largely unchanged. A comparison of treatment agents is difficult, since the agent choice was not controlled and some subjects received concomitant treatment with MTX. Additionally, the discrepancy between dyspnea improvements and other parameters might be partially due to the effect of the treatment on myositis. According to Bunch et al., the AZA+ prednisone combination is favored to prednisone alone in controlling myositis [32]. In the study Maire et al., although the choice of agent was not controlled, the improvement was less robust in the AZA group (58%) than in the patients treated with CYC (72%) and MMF (83%). A lower baseline DLCO was associated with greater deterioration, which may be partially due to severity of the ILD. The UIP pattern appears to be a predictive marker of ILD deterioration, and a greater number of patients in the AZA-treated cohort displayed this pattern. Notably, both studies have revealed superior treatment responses in patients with OP and NSIP. In one case report, which did not meet our criteria, the addition of AZA facilitated a stable lung condition for 15 months following CYC induction and prednisolone was tapered in a patient with dermatomyositis-NSIP [33]. Another case report of a patient with dermatomyositis-OP described an excellent response to steroids and AZA, with gradual tapering over two years. The patient remained off-medications [34]. Researchers have not clearly determined whether the response is partially or entirely related to its impact on myositis.

Deheinzelin et al. showed a noticeable improvement in seven of 11 subjects with SSJ who were treated with AZA, but steroids were administered to six subjects. Of the responders, the researchers were unable to clearly determine the number of subjects that received concomitant steroids. The short follow-up duration made the assessment of the true effect of AZA challenging. Furthermore, the outcomes were similar in patients who had received steroids alone, casting doubt on the role of AZA. The study by Roca et al. used a sample size that was too small to judge the effectiveness of AZA, CYC, or MMF. Among the patients who received steroids alone, the UIP pattern and older age were associated with deterioration and less treatment responses; both of which were compatible with the findings reported by Adevano et al. and Maire et al., although these studies investigated patients with different background CTDs.

SSC-ILD has been more extensively scrutinized more than other CTDs, as the ILD prevalence is the highest in patients with this condition, reaching up to 50%. The most frequently observed ILD pattern is NSIP (fibrotic-NSIP in 90%), which appears to share similarities with the UIP pattern [35]. Dheda et al. did not observe statistically significant effects of the combination of AZA+ prednisone. Berezne et al. reported improved and stabilized parameters of 70% and 51.8%, at six and 24 months, respectively. This improvement in a short period clearly confirms the essential effect of CYC before it gradually decreases, thus undermining the effect of AZA. Furthermore, the possibility of spontaneous remission cannot be excluded. One group that exhibited stabilization after CYC and refused further treatment (n=4) also showed a comparable response to the AZA group. These observations question the effectiveness of AZA. Meanwhile, Poormoghim et al. reported a statistically significant desirable effect of AZA compared to CYC, but the baseline characteristics of the patients were different. Thus, a comparison between AZA and CYC would be unfair. The CYC group had more diffuse-SSC and a shorter duration of the disease; both of which are recognized as poor prognostic factors [36,37]. However, AZA should be considered in patients with favorable prognostic characteristics, particularly in situations where the use of other agents is inadvisable. In the study by Ludicci et al., while AZA produced a more sustained response in CYC responders compared to the inferior response to MMF in CYC nonresponders, its impact is likely to be related to CYC responsiveness, rather than the maintenance agent. Both groups displayed a gradual worsening of lung function at 10 months (the change was more substantial in the CYC nonresponder group that subsequently received MMF), which affirms that the CYC responsiveness was more of a determinant than any particular maintenance agent. Furthermore, CYC nonresponsiveness was the only marker predicting a deterioration of lung function. Thus, AZA has little real impact, if any. Those findings are compatible to the data reported in the study by Berezne. The FAST study by Hoytes et al. failed to achieve a statistically significant difference between the AZA and placebo groups after CYC induction. We did not include two other studies evaluating the effectiveness of AZA in improving PFT in patients who lacked an established ILD diagnosis. Nadashkevieh et al. [38] retrospectively compared CYC with AZA in 30 subjects per cohort, with serial evaluations for up to one year. FVC/DLCO remained stable in the CYC group, while the AZA group experienced worsening. Paone et al. [39] examined the effect of AZA after a CYC pulse on 13 subjects, with re-evaluation in one year. The result showed sustained FVC/DLCO. However, in the effect of AZA on this parameter is difficult to assess, since the effects of CYC persist for six months after CYC interruption, which was clearly observed in the study by Brenzine et al., as well as in the SLS study [40].

In summary, no clear conclusion of AZA effectiveness can be drawn, given the low quality and heterogeneity of the data. Nevertheless, AZA does not appear to surpass CYC or MMF in this unique population. These findings must be confirmed in larger RCTs. In contrast to the current knowledge, our results suggest the new finding that treatment responses depended to a greater extent on the ILD histopathological pattern, rather than the hypothesis that treatment responses largely depend on the CTD subtype, which are relatively less favored in patients with UIP, fibrotic-NSIP, and ALP than in patients with OP, regardless of the CTD background. One report inspected the similarities between RA-UIP and idiopathic pulmonary fibrosis (IPF). Although some pathological patterns occur more prominently in IPF, none of these
patterns were unique or mutually exclusive [41]. An interesting, recently published report investigated the association between the expression of the MUC5B gene in patients with RA-ILD; a variant in the promoter of this gene is considered the strongest risk factor for the development of IPF. The study included 620 patients with RA-ILD, 614 patients with RA without ILD, and 5448 unaffected controls, which were obtained from eight case series in seven countries. The MUC5B promoter variant was associated with RA-ILD and more specifically with UIP [42]. A review of studies using animal models and primary human cells showed the presence of more similar mediators and biomarkers between SSC-ILD and IPF than was previously believed [43]. Subsequently, this resemblance has prompted speculation that fibrotic-NSIP represents a variant of UIP [44]. This hypothesis was confirmed in our analysis; the presence of UIP was a poor indicator of AZA responsiveness, regardless of CTD type. Unlike IPF, the possibility of spontaneous improvement has been reported in patients with CTD-ILD, but not IPF [35-37]. This finding is consistent with the results of the landmark trial that has disputed any beneficial effects of AZA on IPF, not to mention the harm it clearly caused [45]. In patients with ALP, no added benefit was observed after the addition of AZA to corticosteroids. In fact, based on the literature, AZA itself can worsen/induce ILD, particularly AIP and less commonly UIP; the latter was reported more frequently in a posttransplant population [28,46,47]. Conversely, AZA is still a valuable option for patients with OP and cellular-NSIP. AZA is also regarded as an excellent drug for cryptogenic-OP [48,49], but is much less beneficial for fibrotic-NSIP [35-37], which emphasizes our observation that the treatment response may depend on the ILD pattern to a greater extent than the CTD background. Astonishingly, this hypothesis was confirmed for CYC and MMF, when administered to patients with idiopathic ILDs and CTD-ILD. Historically, CYC has been reserved for severe cases of CTD-ILD, yet its safety profile has always been a limitation. CYC was a beneficial treatment for IPF exacerbation in previous studies [50,51]; currently, it is being investigated in the phase III Cyclophosphamide for Acute Exacerbation of IPF Trial. The evidence that MMF represents a valuable and relatively safe option for idiopathic and CTD-related ILD is accumulating. In a retrospective study of 41 subjects with IPF, MMF induced a trend toward a reduced rate of FVC decline compared to the prednisone, AZA, and/or N-acetylcysteine regimens and placebo group. The SLS-II trial has confirmed that MMF is as efficacious as CYC for SSC-ILD. Therefore, we wonder about the extent of the effectiveness of anti-fibrotic agents for CTD-UIP and fibrotic-NSIP, particularly in patients with RA and SSC, given their similarities with IPF. This question will probably be best answered in the SLS-III trial, which is currently investigating the addition of pirfenidone vs. placebo on subjects with SSC-ILD who are already taking MMF. The findings will further improve our understanding of the therapeutic effects.

Nonetheless, this study has many limitations. The main limitation of our study is directly linked to the limited quality of studies available. Substantial heterogeneity in the various CTD diagnoses and choice of outcome(s) exists, and many of the included studies are case reports or case series. Moreover, some of the results may have been confounded by the concomitant use of other medications. These limitations have made the correlations with our endpoints less certain. Given the risk of selection bias, as the majority of included studies were case reports and series, we do not believe that selection bias will have a major impact on the generalizability. Patients with CTD-ILD represent a very selective group of patients in the ILD population, and subjects included in these studies are relatively representative of the average patients in the target population.

Conclusion
No clear impact of AZA has been identified; yet it exhibits less usefulness than was previously assumed. In contrast to our current understanding, this review suggests that the ILD histopathological pattern appears to be the most important determinant of treatment response and prognosis, and treatment decisions should be based on this feature, rather than the background CTD. AZA is a relatively safe option. More well-designed studies are needed. The recruitment of subjects based on ILD pattern rather than CTD may produce more consistent results.

Conflict of Interest
None

Acknowledgment
We would like to express our sincere gratitude to Dr. Riyadh Alsehli for his unconditional support.

References