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Variables Associated With Response to Therapy in Patients With Interstitial Pneumonia With Autoimmune Features

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Background/Objective: We have limited knowledge regarding characteristics of patients with interstitial pneumonia with autoimmune features (IPAF) that are associated with response to immunosuppression. In this study, we used published IPAF criteria to characterize features associated with response to treatment.

Methods: We conducted a single-center medical records review study of 63 IPAF patients to evaluate for serological, clinical, and morphological characteristics that are associated with response to immunosuppression. Response was defined as % relative functional vital capacity decline of less than 10% and absence of death or lung transplant within the first year of continuous immunosuppressive therapy. Nonparametric measures of association and multivariate logistic regression were used to evaluate the relationship between baseline characteristics and immunosuppressive response.

Results: There was a trend of greater progression among men, ever smokers, those negative for antisynthetase antibodies, and those with usual interstitial pneumonia radiographic pattern, but no statistically significant relationship was found between baseline serological, clinical, or morphological features and response to immunosuppression. Patients on combination therapy with mycophenolate mofetil and prednisone had less disease progression ($p = 0.018$) than those on regimens that did not include both of these medications.

Conclusions: In our cohort, baseline clinical assessment did not identify which patients with IPAF will respond to immunosuppressive therapy. Combination therapy with mycophenolate mofetil and prednisone was associated with lack of disease progression in our IPAF patients, including in IPAF–usual interstitial pneumonia. Further studies are needed to evaluate which IPAF patients would benefit from immunosuppressive therapy, antifibrotic therapy, or a combination of both.

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Interstitial pneumonia with autoimmune features (IPAF) is a recently defined classification aimed at addressing concerns that autoimmunity contributes to diffuse parenchymal lung disease in ways that may be underappreciated by current and more stringent classification criteria for connective tissue diseases (CTDs). It purports to classify, for research purposes, interstitial lung disease (ILD) with autoimmune features, which currently is not accepted into any of the other specified ILD subtypes.[1]

Interstitial lung disease classification relies on the subjective interpretation of clinical, pathologic, and radiographic features to attribute etiology, which results in inconsistencies.[2] This poses challenges for appropriate treatment choice as the latter is driven by underlying disease mechanisms. Current ILD therapy includes antifibrotic medications to target fibrosis or immunosuppressive agents that target inflammation. Idiopathic pulmonary fibrosis (IPF) is primarily treated with antifibrotics, a tactic supported by multiple clinical trials that have demonstrated improvement in progression-free survival and reduction in disease progression,[3–5] whereas immunosuppression in these patients has been shown to increase mortality.[6] In contrast, clinical trial data for immunosuppression in ILD are scarce and primarily extrapolated from the Scleroderma Lung Trials I and II that evaluated cyclophosphamide and mycophenolate mofetil.[7,8] Results from these trials are applied to the management of other CTD-associated ILD (CTD-ILD). However, there are some patients who have interstitial pneumonia and features of autoimmunity but do not fulfill the classification criteria for a CTD, who may also benefit from immunosuppression. In 2015, the European Respiratory Society and the American Thoracic Society created a task force to address the classification and management of these latter patients and coined the term "interstitial pneumonia with autoimmune features" to account for this presentation. They defined IPAF as ILD in persons with autoimmune features who cannot be characterized by other specified ILD subtypes.[1]

The IPAF classification includes 3 domains: serological, clinical, and morphological characteristics.[1] Two of 3 domains must be satisfied to meet the IPAF criteria.[1] The serologic domain consists of specific autoantibodies, the clinical domain consists of signs and symptoms suggestive of CTDs, and the morphologic domain consists of suggestive radiographic and histopathologic patterns or evidence of multicompartment involvement.[1] Nonspecific interstitial pneumonia (NSIP), organizing pneumonia, or lymphocytic interstitial pneumonia patterns on high-resolution computed tomography (HRCT) imaging of the chest or on surgical biopsy are frequently associated with CTD-ILD and are included in the morphologic domain specification. Usual interstitial pneumonia (UIP) pattern is not included as one of the inclusion morphological criteria of IPAF as it is not suggestive of an autoimmune etiology of interstitial pneumonia, despite its frequent association with certain CTDs such

as rheumatoid arthritis. Thus, although UIP is not included as one of the inclusion criteria of IPAF, it is not an exclusion criterion.

Data on the natural history of patients with IPAF is scarce. The majority of studies have aimed to evaluate survival, whereas fewer studies have evaluated prognostic factors in IPAF. Multiple studies have found that overall, survival in IPAF was substantially better than that in IPF[9,10] but worse than in CTD-ILD.[9,11–13] Presence or absence of NSIP or UIP injury patterns may be an important prognostic factor in survival with IPAF patients; NSIP injury pattern has similar survival as CTD-ILD patients,[9] whereas IPAF-UIP patients had survival similar to that in IPF.[9,10] In addition, various factors such as advanced age, history of smoking, and baseline lower diffusing capacity of the lung for carbon monoxide (DLCO) have been found to predict poor outcome in cohorts of IPAF patients.[9,14–17] Higher initial functional vital capacity (FVC) and DLCO at diagnosis and positive antinuclear antibodies (ANAs) above a certain threshold were associated with improved survival and slowed pulmonary function test (PFT) decline in other studies.[11,18] In addition, Black patients with ILD (including IPAF) might have improved survival outcomes compared with non-Black patients.[19] Recently, myositis-specific antibody (MSA) presence in IPAF was identified as a favorable prognostic factor for survival.[20] Although these studies evaluated survival and clinical deterioration during follow-up, they did not evaluate response to immunosuppressive therapy. It remains unclear whether and when IPAF patients should be treated with immunosuppression (upon diagnosis and without awaiting decline in pulmonary function, or upon observation of pulmonary decline). Further, it is important to understand how IPAF-UIP patients, who may be more similar to IPF patients than CTD-ILD, respond to immunosuppression, because immunosuppression leads to increased mortality in IPF.[6] The objectives of this medical records review study are to evaluate the serologic, clinical, and morphologic domains as well as medication regimens that may be associated with response to immunosuppression among IPAF patients.

PATIENTS AND METHODS

Cohort Assembly

This single-center medical records review study was performed at the University of Texas Southwestern Medical Center. Consecutive patients seen in the University of Texas Southwestern Medical Center Interstitial Lung Disease Clinic between January 2005 and April 2019 who met the European Respiratory Society/American Thoracic Society classification criteria for IPAF were identified.[1] The University of Texas Southwestern Medical Center Institutional Review Board approved the study prior to initiation of data extraction (IRB #STU-2019-0913). Patient consent was not obtained for this medical records review study.

Data Collection and Variables

All data were extracted from the electronic medical record (EMR) by a rheumatologist (E.K.J.). A pulmonologist (T.N.A.) and radiologist (K.B.) reviewed HRCT of the chest to classify patients as UIP or non-UIP pattern.

Patients meeting the criteria for IPAF (domains listed below) who have never been on immunosuppression in the past and who were initiated on continuous immunosuppressive therapy (prednisone, mycophenolate mofetil, azathioprine, and rituximab) during follow-up were eligible for inclusion in this study. Continuous immunosuppressive therapy was defined as a period of at least 12 months of therapy with no periods of therapy interruption greater than 4 weeks. Steroid courses, if received as a taper, were not considered a period of continuous immunosuppression. We excluded patients who were on prior or concurrent antifibrotic therapy, those with fewer than 2 clinic visits, those with fewer than 2 PFTs, and those who did not have PFTs available prior to initiation of immunosuppression.

IPAF Serologic Domain

Laboratory data included ANA status based on the published IPAF criteria,[1] antibodies to dsDNA, rheumatoid factor (positive if ≥2 times above the reference value), anti-CCP, antibodies to Ro/SSA, La/SSB, Scl-70, U1-RNP and Smith, PM-Scl, MDA-5, and a panel of MSAs. When 1 or more laboratory data points existed, we utilized first the available chronologically, if prior to or within the first 6 months of starting immunosuppression or, if an antibody turned positive, the first positive value of a titer within 6 months of initiation of immunosuppression.

IPAF Clinical Domain

Clinical data from pulmonary clinic, ambulatory care, and rheumatology progress notes included presence or absence of provider diagnosed distal digital fissuring, distal digital tip ulceration, inflammatory arthritis or polyarticular morning stiffness ≥60 minutes, palmar telangiectasias, Raynaud phenomenon, unexplained digital edema, and unexplained fixed rash on digital extensor surfaces ("mechanic hands").[1] The clinical component was considered present (yes/no) if noted prior to or during the treatment period.

IPAF Morphologic Domain

Morphological data of HRCT pattern and presence of multicompartment involvement were included based on review of radiology and procedural reports (HRCT, x-ray, echocardiograms, right-sided heart catheterization [RHC]) and the pulmonary clinic notes. First, chronologically available radiographic data were included, as long as it was noted prior to or within the treatment period. If a data point turned positive during the treatment period (i.e., new pleural effusion), it was also considered present. The HRCT was independently reviewed by an expert thoracic radiologist (K.B.) and pulmonologist (T.N.A.). In the case of discrepancy, imaging and procedural results were used to reduce the risk of misclassification. Multicompartment involvement was defined according to published definitions and included unexplained intrinsic airway disease, pleural or pericardial disease, and pulmonary vasculopathy requiring pulmonary artery mean pressure ≥25 mm Hg and wedge pressure <15 mm Hg on RHC, or estimated right ventricular systolic pressure ≥40 mm Hg by echocardiography.[13] Airway disease was only considered unexplained if present in a nonsmoker, due to risk of misclassification of chronic obstructive pulmonary disease due to smoking. As biopsies were inconsistently obtained prior to or during the treatment period (n = 31), the histopathologic data were not routinely collected for inclusion in the domain characteristics.

Demographics

Demographic data included age at ILD diagnosis, gender, race/ethnicity as documented in EMR, and smoking status (never/ever). Interstitial lung disease diagnosis date was considered to be the time point at which ILD was first observed on imaging. Race and ethnicity were documented in the EMR using prespecified categories (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, unavailable/unknown, some other race, or declined, and Hispanic or Latino, non-Hispanic/Latino, declined, or unknown) and not confirmed with the patient.

PFT Data

Pulmonary function test data included FVC, FEV_1 (forced expiratory volume in the first second), FEV_1/FVC ratio, and DLCO expressed as percentages of predicted as well as absolute values. Two sets of PFTs were evaluated in this analysis. Baseline PFTs were considered first available PFTs prior to continuous immunosuppression initiation. We included PFT values at 12 months after starting continuous immunosuppression, with a range of 3 months prior to or after the 12 month time point, whichever date was closest temporally.

Medication Use

Data on immunosuppressive therapy (prednisone, azathioprine, mycophenolate mofetil, and rituximab) including types of medications and exposure dates were extracted. The entry date for the study was time of first immunosuppression exposure leading to the first continuous year of immunosuppression (for which we had PFTs prior to initiation). Time (in years) from diagnosis to start of continuous immunosuppression was calculated.

Additional Data Collected

Values for erythrocyte sedimentation rate, C-reactive protein, creatine kinase (CK), and aldolase were also collected, utilizing the first available chronologically, if prior to or within the first 6 months of starting immunosuppression. History of malignancy, presence of sicca, and gastroesophageal reflux/esophageal dysmotility was also collected from progress notes, if noted prior to or during the treatment period.

Primary Outcome

The primary outcome was proportion of patients on immunosuppressive therapy with absence of significant progression during treatment. Based on the literature, significant progression was defined as annual relative decline in FVC ≥10% predicted, death, or transplant within the first year of initiating immunosuppressive treatment.[21]

Statistical Analysis

The cohort was separated into 2 groups: those with ≥10% relative FVC decline, death, or lung transplant (progressors) and those with <10% relative FVC decline (nonprogressors) at 12 months after immunosuppression initiation. Categorical variables were expressed as counts with percentages, and continuous variables were expressed as mean with SD. We evaluated for serological, clinical, and morphological characteristics that are associated with response to immunosuppression using χ^2 test, Fisher exact test, or Mann-Whitney *U* test, as appropriate. All tests were 2-sided. We similarly evaluated for differences in immunosuppressive treatment patterns between progressor and nonprogressor groups. Any comparison with a p value of 0.05 or less (2-sided) was considered as a variable associated with progression in a multivariate logistic regression along with UIP radiographic patterns. The sample size in the smaller group (n = 12) allowed a model with 2 variables associated with progression. Odds ratios and their 95% confidence intervals (CIs) were calculated using logistic regression to compare the 2 groups. No adjustment was made for multiple comparisons or for missing data. In the UIP/non-UIP radiographic pattern subgroups, we also evaluated for differences in the proportion of progressors and any serological, clinical, and morphological characteristics, as well as differences in treatment patterns. Missing data were not analyzed; sample sizes are listed where appropriate.

We utilized univariate logistic regression to evaluate for baseline variables associated with categorical progression. Baseline predictor variables included presence of serological, clinical, and morphological domains of IPAF criteria; presence of UIP radiographic pattern; age at ILD diagnosis; age at immunosuppression initiation; duration of time from diagnosis to immunosuppression initiation; gender; race/ethnicity; smoking status; baseline %FVC; baseline %DLCO; immunosuppressive medication regimens; erythrocyte sedimentation rate; C-reactive protein; CK and aldolase levels; presence of malignancy; presence of sicca; and presence of gastroesophageal reflux/esophageal dysmotility. Variables selected via the univariate test with a $p < 0.05$ were evaluated using multivariate logistic regression while controlling for UIP radiographic presence, given poor prognosis associated with UIP pattern.[9] Because of small sample size, adjusting for other confounders known to be associated with ILD outcomes (age at ILD diagnosis, gender, race/ethnicity, smoking status, baseline %FVC, baseline %DLCO) could not be performed. $p < 0.05$ was considered significant. Software package Stata version 14 (StataCorp, College Station, TX) was used for all statistical computations.

RESULTS

A cohort of patients meeting the 2015 IPAF criteria[1] (n = 200) was created. We excluded patients who were never on immunosuppressive treatment (n = 49) or those on immunosuppressive medications prior to or at first available PFTs (n = 60), those with fewer than 2 office visits (n = 5), those who did not have available PFTs that spanned the first year of consecutive immunosuppressive therapy (n = 14), those who had more than 4 weeks' therapy interruption during the first year of immunosuppression (n = 2), and those who were on previous or concurrent antifibrotic medication treatment (n = 7). We identified 63 patients who fulfilled the aforementioned criteria.

Among the 63 patients included in this cohort, 19.05% (n = 12) progressed, and 80.95% (n = 51) did not progress during immunosuppressive treatment. Among those who progressed, 3 patients died during follow-up (2 deaths from unknown cause, 1 from respiratory cause), and 1 received a lung transplant.

Baseline Characteristics

Interstitial pneumonia with autoimmune feature serological classification criteria were met in 96.83% of patients, clinical in 42.86%, and morphological in 100.00% patients (data not shown). The radiographic UIP pattern was seen in 26.98% of the patients (Supplemental Table 1, http://links.lww.com/RHU/A390). The mean age at ILD diagnosis was 58.83 ± 10.76 years. Overall, 74.60% of the cohort was female. White, non-Hispanic patients comprised 60.32% of the cohort; Black, non-Hispanic patients comprised 17.46%; 17.46% were Hispanic, and 4.76% were Asian patients. No patients were identified as Native American or Alaska Native, Native Hawaiian, or Other Pacific Islander; 42.86% of the patients were ever smokers. The mean baseline FVC was 59.04% ± 14.53%, and the mean DLCO was 41.87% ± 16.67% (Supplemental Table 1, http://links.lww.com/RHU/A390).

Baseline phenotypic features, including the individual variables within the IPAF serologic, clinical, or morphologic domains, were not associated with response to immunosuppressive therapy in patients (Supplemental Tables 1, http://links.lww.com/RHU/A390, and 2, http://links.lww.com/RHU/A391), although there was a trend of greater progression among men, ever smokers, those negative for antisynthetase antibodies, and those with UIP radiographic pattern. There were no Black, non-Hispanic patients among those who progressed, but the difference was not statistically significant.

Patients With UIP Radiographic Pattern

Patients with UIP radiographic pattern (n = 17) were significantly older than patients with non-UIP pattern at diagnosis (mean age at diagnosis, 64.77 vs. 56.64 years; $p = 0.0058$). Patients with UIP pattern had a higher baseline %FVC and %DLCO than patients with non-UIP radiographic pattern, but despite that, there was a higher proportion of progressors in the group of patients with UIP (29.41% vs. 15.22%, $p = 0.203$) (Supplemental Table 3, http://links.lww.com/RHU/A392). There was a statistically higher proportion of patients who were SSB antibody positive among patients with UIP radiographic pattern (33.33% vs. 2.17%, $p = 0.003$). Other features, including treatment patterns, did not differ significantly between the groups (data not shown).

Immunosuppressive Treatment

The median duration to initiation of continuous immunosuppression after diagnosis was 1.23 years (interquartile range, 0.37–2.35 years). Patients were treated with prednisone, mycophenolate mofetil, and azathioprine, either alone or in combination. During the treatment period, 84.13% patients were treated with prednisone, most commonly in combination with mycophenolate mofetil (69.84%) or azathioprine (20.63%); 6.35% patients received treatment with prednisone as well as sequential treatment with mycophenolate mofetil and azathioprine throughout the year of follow-up. One person was treated with rituximab in addition to prednisone and mycophenolate mofetil.

A statistically significant proportion of patients treated with mycophenolate mofetil and prednisone during the first year of therapy did not progress (76.47% vs. 41.67%, $p = 0.018$), with odds ratio 0.22 (95% CI, 0.059–0.82). In multivariate logistic regression analysis controlling for presence of UIP radiographic pattern, we found that any regimen that included mycophenolate mofetil/prednisone during the first year of immunosuppression was associated with nonprogression over the first year of therapy.

DISCUSSION

In this medical records review study, we aimed to identify factors associated with response to immunosuppression, which might inform the decision on initiation of immunosuppressive therapy. However, we did not identify any serological, clinical, or morphological characteristics that were associated with disease progression in immunosuppressed IPAF patients, suggesting that baseline clinical assessment cannot be used to identify which patients will respond to immunosuppression. We did find that combination immunosuppressive therapy with mycophenolate mofetil and prednisone was associated with lack of disease progression in our cohort.

Other studies have sought to identify variables associated with decreased disease progression in immunosuppressed IPAF patients. In a retrospective analysis of 92 patients classified with IPAF, univariate analysis showed that presence of scleroderma-associated antibodies (ANA nucleolar pattern, ANA centromere pattern, anti-RNP, and anti-Scl-70) and SSB antibodies was associated with less progression in patients on immunosuppression.[16] In our study, we did not identify any such markers. We did find non–statistically significant higher proportion of men and smokers and a lower proportion of Black, non-Hispanic patients in the progressor group, a finding reported by others.[19,22]

Our practice mirrors what has been considered standard of care for the field, meaning that non-IPF patients in which we suspect an immunologic basis are treated with immunosuppression. Our ILD clinic preferentially uses immunosuppressive regimens consisting of azathioprine, mycophenolate mofetil, and prednisone. Use of rituximab is relatively rare and is reserved as second-line therapy. In our cohort, patients treated with combination therapy of mycophenolate mofetil and prednisone were less likely to have disease progression. Chartrand and colleagues[23] published data on their retrospective cohort of 56 IPAF patients, the majority (approximately 80%) treated with mycophenolate mofetil and prednisone combination. Their cohort demonstrated little %FVC decline and no deaths during a mean 285 days of follow-up. A study by McCoy et al.[24] found that mycophenolate exposure correlated to decrease in the rate of FVC decline in a cohort of IPAF patients. We did not find the same favorable outcome with mycophenolate mofetil exposure in our cohort in the absence of prednisone exposure.

We found that in our multivariate logistic regression model, mycophenolate mofetil/prednisone exposure was associated with the likelihood of nonprogression after adjusting for UIP radiographic pattern (a potential confounder documented in the literature).[16] This suggests that combination therapy of mycophenolate mofetil and prednisone may be associated with lack of progression even in IPAF-UIP patients. This finding is novel as there are no studies specifically evaluating IPAF-UIP response to immunosuppression.

We acknowledge several limitations to our study. The small size of our cohort limited our ability to meaningfully assess for confounders that may influence our outcomes. Sample size was limited, in part, due to rigorous exclusion criteria, allowing for greater internal validity of our sample. Inherent limitations to medical records review studies include misclassification bias and missing data. We have attempted to reduce misclassification bias (such as morphological features seen on imaging) by including specialists on the team who correlate the EMR reports with the clinical findings. The %DLCO was significantly reduced in our cohort, raising possibility that undiagnosed pulmonary arterial hypertension could be playing a role in the results. However, evaluation for pulmonary arterial hypertension was avidly pursued in our cohort. All but 7 patients with %DLCO less than 50% had at least 1 transthoracic echocardiogram. Furthermore, of a total of 50 patients who had a transthoracic echocardiogram, only 6 of those who had right ventricular systolic pressure of more than 25 mm Hg and less than 40 mm Hg did not receive RHC. Thus, we believe that mild pulmonary hypertension, if present and undiagnosed, would not play a significant role in our results. In addition, our data are derived from one academic clinical setting and cannot be extrapolated to other clinical settings or geographic sites where there may be variation in treatment practices.[25] Also, given our study design, we cannot conclude that the patients' progression status could be solely attributed to immunosuppressive regimen or to other unique features associated with the specific IPAF course. Future larger, multi-institutional cohort studies may help mitigate this issue.

Notably, while we gathered data from multiple domains relevant to IPAF, there may be additional, more specific, serological, clinical, and morphological features that were unmeasured. Recent data suggest that MDA-5 and anti-Ro52 antibodies play a role in ILD.[26,27] As these antibodies were not routinely checked, and none of the patients had MDA-5 antibody positivity on labs, these data were not included in our study but would be important to collect in future studies.

Our study had several strengths. We were able to capture granular data on multiple variables of interest within the current IPAF classification scheme. We selected an outcome consistent with other studies in the field, which makes our results more interpretable in the context of results from these other cohorts.[21,28] Our cohort includes men and racial and ethnic minorities, allowing us to extend our understanding of IPAF response to immunosuppression to different populations.

In conclusion, our results suggest that a combination therapy with mycophenolate and prednisone is associated with decreased disease progression in IPAF during treatment, including in IPAF-UIP patients. Prospective studies are needed to further evaluate various medication regimens in IPAF. Importantly, our findings suggest that baseline clinical assessment may not reliably identify which IPAF patients will progress while on immunosuppressive therapy. Given that IPAF is a relatively new entity and includes a heterogeneous group of patients, further research is needed to fully elucidate which tests (serological, radiological, procedural) are needed for an accurate diagnosis and, further, how these might help us determine appropriate immunosuppressive therapy, and emphasize the need for education of clinicians, including interdisciplinary teams that routinely care for IPAF patients.

KEY POINTS

- Baseline clinical characteristics cannot be reliably associated with response to immunosuppressive therapy in patients with IPAF.
- Combination therapy with mycophenolate mofetil and prednisone was associated with nonprogression of lung disease in our cohort.

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