Respiration

Editorial Comment

Respiration 2020;99:930–931
DOI: 10.1159/000509612

Received: June 19, 2020
Accepted: June 22, 2020
Published online: October 6, 2020

Azathioprine for Connective Tissue Disease-Associated Interstitial Lung Disease: In Search for Evidence-Based Medicine

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Lung involvement in collagen tissue diseases is one of the most worrisome complications as it is related to increased morbidity and mortality. Almost every CTD can affect the lung. The nature of interstitial lung disease (ILD) depends on the underlying CTD, yet, as mentioned before, any type of lung involvement negatively impacts quality of life and survival [1]. Despite the fact that lung involvement has been thoroughly studied and defined in the setting of CTD [2–4], there is a significant unmet need in terms of management [5]. There is a striking lack of randomized controlled trials in CTD-ILD. Most recommended therapeutic approaches are based on expert opinion and small trials. Under these circumstances, every piece of information can be extremely useful as it solidifies evidence-based medicine in the field of CTD-ILDs.

In this issue of *Respiration*, Börner et al.[6] offer such information. They describe their experience regarding the use of azathioprine in 56 patients with CTD-ILD. The population was heterogeneous consisting of 21 patients with rheumatoid arthritis, 14 patients with systemic sclerosis, 10 patients with polymyositis/dermatomyositis, 4 patients with undifferentiated CTD, 3 patients with mixed CTD, 2 patients with Sjogren's syndrome, and 2 patients with psoriatic arthritis. The majority of patients (70%) exhibited a nonspecific interstitial pneumonia (NSIP) pattern at HRCT that was followed by a usual interstitial pneumonia pattern (16%) and an organizing pneumonia pattern (4%). In the remaining cases, the pattern of lung fibrosis was indeterminate. The median follow-up time was 35 months (IQR: 3–109) and the median treatment duration was 34 months (IQR: 3–105). There was no statistical significance in the course of neither FVC nor DLco during the study period. Specifically, mean FVC was 66 ± 18% pred at the initiation of treatment and 63 ± 18% pred at the last follow-up visit ($p = 0.2$). Mean DLco was 42 ± 19% pred at the initiation of treatment and 40 ± 17% pred at the last follow-up visit ($p = 0.25$). The majority of patients (66%) exhibited stabilization or improvement, while 34% progressed. Changes in FVC or DLco were not different between patients with a usual interstitial pneumonia or an NSIP imaging pattern. It is worth emphasizing that in a subset of patients, there were available data regarding the course of FVC (21 patients) and DLco (16 patients) 6 months prior to the initiation of treatment with azathioprine. In these patients, the mean decline of FVC and DLco in the 6 months prior to the initiation of azathioprine was statistically significant (for FVC: 9 ± 2% pred, $p < 0.001$ and for DLco: 8.5% ± 2% pred, $p = 0.012$). Six months after the initiation of azathioprine, stabilization was achieved regarding the mean change for both FVC% (1 ± 1.4% pred, $p = 0.468$) and DLco (−2.6 ± 1.8% pred, $p = 0.142$). More

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than half of the patients (52%) discontinued azathioprine, with tolerability posing a significant challenge. Specifically, adverse events leading to definitive discontinuation were observed in 30% with the leading cause being hepatotoxicity, seen in 14%. Treatment with azathioprine did not have any impact on the levels of serum KL-6 and LDH.

An important message from this study is the significance of individualizing treatment. Although there was no statistically significant change in FVC% pred and DLco% pred during the study period, the majority of patients (66%) exhibited stabilization or improvement. Thus, it is important to tailor any treatment to the response of the individual patient. In the current era, it seems impossible and probably utopian to find a "*one size fits all*" treatment. The most important point of this study is that in some patients (21 for FVC and 16 for DLco), there were available pulmonary function tests data 6 months prior to the initiation of treatment with azathioprine. In this period of 6 months before the start of treatment, there was a statistically significant decline in FVC% pred and DLco% pred. The course of FVC% pred and DLco% pred stabilized 6 months after the initiation of azathioprine, providing evidence for its beneficial effect. Unfortunately, due to the relative small sample and the heterogeneity of the studied cohort, no robust conclusions can be drawn regarding its efficacy in specific subsets of patients (e.g., based on the underlying CTD or the HRCT pattern of involvement). Nevertheless, one can speculate that the predominance of NSIP [7] in the study population could explain this beneficial result.

A major unmet need is the progressive course of fibrotic CTD-ILD that can resemble that of idiopathic pulmonary fibrosis, especially in patients with rheumatoid arthritis-related ILD [8,9]. It is important to keep in mind that while in idiopathic pulmonary fibrosis the role of inflammation is controversial [10], in CTD-ILD, it plays an evident role. This highlights the need for an approach that will cover both aspects of inflammation and fibrosis. The above approach is even more important in light of the recent INBUILD study [11] in which nintedanib reduced the annual rate of decline in FVC in patients with progressive fibrotic ILD. A significant proportion of these patients (25.6%) had autoimmune ILD. In patients with CTD-ILD covering both aspects of ongoing inflammation and fibrosis is important. The SENCIS trial [12] is a characteristic example in which the combination of immunomodulation (mycophenolate mofetil) and antifibrotic (nintedanib) provided the best result, with respect to each agent separately. The study by Börner provides important evidence that azathioprine can be a useful asset in our arsenal. Taking into consideration the significant additional morbidity and mortality in CTD through CTD-ILD, a combined effort between national and international rheumatology and respiratory associations should be discussed. The aim should be to collect lung function data of patients with CTD upon diagnosis in order to get a valid overview of the onset and early development of CTD-ILD. Only through such efforts will we be able to tackle this complication of CTD early on and hopefully improve the outcome for patients. Further multicenter, randomized controlled studies are needed in order to achieve an evidence-based management of CTD-ILD.

Conflict of Interest Statement

All authors have no conflicts of interest to disclose.

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