Treating CTDs Related Fibrotic ILDs by Immunosuppressants: “Facts and Faults”

Spyros A. Papiris · Konstantinos Kagouridis ·
Georgia Papadaki · Likurgos Kolilekas ·
Effrosyni D. Manali

Received: 4 August 2013 / Accepted: 22 October 2013 / Published online: 12 November 2013
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Abstract Fibrotic interstitial lung diseases (ILDs) are commonly encountered in scleroderma where they significantly influence prognosis. The mainstay of treatment in idiopathic fibrotic ILDs for the past 30 years was based on the combined administration of prednisone and cyclophosphamide (CYC) or prednisone, azathioprine plus *N*-acetyl cysteine, recently proved ineffective and harmful. Rheumatologists also despite “facts” showing that CYC treatment has no beneficial impact on fibrotic ILDs in scleroderma continue to commit the same, in a manner of speaking, “faults” by “treating their fibrotic ILDs by immunosuppressants.” In this issue of the journal, Panopoulos et al. (Lung, 191, 483–489, 2013) recognizing the minimal effect of CYC on fibrotic ILDs in scleroderma patients and the increased use in clinical practice of mycophenolate mofetil (MMF) as an alternative, report that MMF use to replace CYC in this setting is not supported, confirming that restoration of purely fibrotic damage in the lungs remains one of the most challenging fields in medicine.

Keywords Fibrotic interstitial lung diseases · Scleroderma · Immunosuppressants · Mycophenolate mofetil · Cyclophosphamide · Pulmonary fibrosis · Treatment

Fibrotic nonspecific interstitial pneumonia (f-NSIP) and usual interstitial pneumonia-type pulmonary fibrosis (UIP/PF) are commonly encountered in connective tissue diseases (CTDs) and especially in scleroderma where they significantly influence prognosis [1, 2]. In scleroderma, although f-NSIP is more commonly expressed than UIP/PF, prognosis is not related to the specific interstitial lung disease (ILD) subtype but to the severity of lung damage as reflected by the decline in diffusion capacity [3]. Indeed, in scleroderma patients the distinction between UIP/PF and f-NSIP is of minor clinical importance, because most patients with f-NSIP pattern definitely progress to fibrosis regardless of treatment [4]. On the other hand, the kinship between idiopathic NSIP and idiopathic pulmonary fibrosis (IPF) in the non-CTDs context is a matter of discussion [5, 6].

The mainstay of treatment in idiopathic fibrotic ILDs and especially in IPF for the past 30 years was based on the combined administration of prednisone, azathioprine plus *N*-acetyl cysteine or prednisone, and cyclophosphamide (CYC), although individual physicians raised concern about the effectiveness and the significant toxic side effects of this regimen [7, 8]. Concern was fully satisfied recently when an interim analysis of the PANTHER-IPF study proved the ineffectiveness and harmfulness of the above combination [9]. Following the same pathway of thinking rheumatologists despite “facts” showing that CYC treatment has no beneficial impact on fibrotic ILDs in scleroderma patients continue to commit the same, in a manner of speaking, “faults”: “treating CTDs related fibrotic ILDs by immunosuppressants” [10, 11].

S. A. Papiris (✉) · K. Kagouridis · G. Papadaki ·
L. Kolilekas · E. D. Manali
2nd Pulmonary Medicine Department, “Attikon” University
Hospital, Athens Medical School, National and Kapodistrian
University of Athens, 1 Rimini Street, 12461 Haidari, Greece
e-mail: papiris@otenet.gr

K. Kagouridis
e-mail: konstantinos.kagouridis@gmail.com

G. Papadaki
e-mail: geo4pap@gmail.com

L. Kolilekas
e-mail: lykol@yahoo.gr

E. D. Manali
e-mail: fmanali@otenet.gr

In this issue of the journal, Panopoulos et al. [12] recognizing the minimal effect of CYC on fibrotic ILDs in scleroderma patients and the increased use in clinical practice of mycophenolate mofetil (MMF) as an alternative, report the results of a 2-year case control study comparing the effect on respiratory and imaging parameters of MMF or CYC treatment versus controls. The authors conclude that MMF use to replace CYC in this setting is not supported. More precisely, they found that lung function parameters did not change significantly in MMF, CYC, or controls after 1 or 2 years of treatment. MMF treatment was associated to significant deterioration of lung computed tomography findings at 2 years, although the disease burden of ILD at baseline was higher in patients receiving CYC. The above findings are apparently in contrast with the results of a recent retrospective study by Fisher et al. [13] who report stabilization or even improvement in pulmonary physiology parameters, such as FVC and DLCO in a cohort of 125 patients with CTD-related ILDs, including scleroderma, as well as with few other studies published previously [14, 15].

The “strongest and cleanest end-point” for phase three clinical trials in fibrotic ILDs is all-cause mortality [16]. However, mean survival in patients with CTD-related fibrotic ILDs is referred to be over 10 years [17]; thus, clinical trials lasting 2 or 3 years could not possibly show a difference in mortality. The use of surrogate to mortality endpoints has been heavily criticized in IPF trials where the change in pulmonary physiology parameters has been used as such [16]. It is now clear that even marginal declines in FVC between 5 and 10 % do not equal stability as previously thought but are related to progression of the disease and increased risk of death. [18]. Even lower declines 2–6 % in FVC are associated with increased risk of death. However, in CTD-ILDs trials not only a deceleration of decline or stabilization but also an improvement in pulmonary physiology parameters is reported, an apparently encouraging sign possibly reflecting “restoration” of lung damage [13]. However, this finding should be interpreted cautiously for the following reasons. First of all, the natural history of CTDs related fibrotic ILDs appears extremely variable for reasons not yet elucidated. There are patients who remain stable for a long period of time and others that present slow (most of them) or rapid (a minority) respiratory decline. Occasional patients also may experience the devastating development of the acute exacerbations of fibrotic ILDs at any time point of the above clinical courses [19]. The nonfrequent occurrence of acute exacerbations in scleroderma fibrotic ILDs might relate to the lesser exposure of these patients to the toxicity of steroids because of the fear of renal crisis development [20]. Therefore, spontaneous stabilization of fibrotic ILD for long periods may influence the interpretation of the results in therapeutic

interventions that use surrogate end points. Secondly, it is not uncommon to encounter in lung biopsies from fibrotic interstitial pneumonias the organizing pneumonia pattern which either “by stands” or clinically overlaps the fibrotic pattern of UIP or fibrotic NSIP [21, 22]. Organizing pneumonia detected in such cases is reversible with immunosuppressants and its resolution could correspond to the marginal improvement seen in the pulmonary physiology parameters. Such an improvement in no way corresponds to a “restoration” of fibrotic damage. However, surgical lung biopsies are not widely used in scleroderma patients as it is an invasive method related to morbidity and provides histological findings of little prognostic value [23]. Last but not least, interstitial chronic inflammation, although a modest feature of fibrotic NSIP in scleroderma-ILDs [3] could be suppressed by immunosuppressants and corticosteroids, giving a further explanation of the minor beneficial effects reported. The study by Fisher et al. [13] refers indeed to a heterogeneous population where the presence of ILDs that are not fibrotic could influence the results of the applied treatment.

The study by Panopoulos et al., as reported by the authors, is not an intention to treat analysis and potential patient’s selection biases could influence the results. Eight of ten patients in each group had already completed 24 months of treatment. Evaluation of ILD in the present study is done through pulmonary function tests and HRCT scoring, whereas BAL and histology characteristics are not available. The requirement of at least 1 year of treatment could have selected a group of patients where all “reversible” parameters of scleroderma related ILDs were already suppressed, shedding that way light on the fact that restoration of purely fibrotic damage in the lung remains one of the most challenging fields in medicine.

In conclusion, what do we know up to now? We know that fibrotic ILDs develop in more than two thirds of scleroderma patients with lung involvement. We know that all the drugs that have been used for CTD related fibrotic ILDs are potent immunosuppressors with well-described toxicity. We also know that in the archetype of fibrotic ILDs, the IPF, all these drugs not only proved ineffective but also harmful. We understand that in the context of autoimmune milieu of CTDs related fibrotic ILDs the most attractive treatment approach would be immunosuppression. However, we are wondering what are the facts to support this strategy? Rheumatologists should learn from pulmonologists mistakes and avoid fixing a fibrotic lung by continuously attacking it with drugs of no proven efficacy but of fully proven lung toxicity and predisposition to severe infections. Even more importantly, rheumatologists should be enlightened and intrigued by the controversial and modest results of their own studies concerning the treatment of fibrotic ILDs in scleroderma patients and

proceed to the development of well-designed clinical trials based on the “*primum non nocere*” concept of Hippocrates, on the distinction of fibrotic from nonfibrotic ILDs and on the selection of new drugs that could substantially change the natural history of fibrotic ILDs as documented by the interpretation of data under the prism of robust and clinically relevant endpoints.

Conflict of interest None.

References

- Papiris SA, Vlachoyiannopoulos PG, Maniati MA, Karakostas KX, Constantopoulos SH, Moutsopoulos HH (1997) Idiopathic pulmonary fibrosis and pulmonary fibrosis in diffuse systemic sclerosis: two fibroses with different prognoses. *Respiration* 64(1): 81–85
- Antoniou KM, Margaritopoulos G, Economidou F, Siafakas NM (2009) Pivotal clinical dilemmas in collagen vascular diseases associated with interstitial lung involvement. *Eur Respir J* 33: 882–896
- Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, Haslam PL, Vassilakis DA, Black CM, du Bois RM (2002) Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med* 165(12):1581–1586
- Remy-Jardin M, Remy J, Wallaert B, Battaille D, Hattron PY (1993) Pulmonary involvement in progressive systemic sclerosis: sequential evaluation with CT, pulmonary function tests, and bronchoalveolar lavage. *Radiology* 188:499–506
- Flaherty KR, Travis WD, Colby TV et al (2001) Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med* 164:1722–1727
- Maher TM, Wells AU, Laurent GJ (2007) Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms? *Eur Respir J* 30(5):835–839
- American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001 (2002) *Am J Respir Crit Care Med* 165:277–304
- Du Bois RM (2010) Strategies for treating idiopathic pulmonary fibrosis. *Nat Rev Drug Discov* 9(2):129–140
- Idiopathic pulmonary fibrosis clinical research network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ (2012) Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 366(21):1968–1977
- Nannini C, West CP, Erwin PJ, Matteson EL (2008) Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. *Arthritis Res Ther* 10:R124
- Walker KM, Pope J (2012) Treatment of systemic sclerosis complications: what to use when first line treatment fails—a consensus of systemic sclerosis experts. *Semin Arthritis Rheum* 42:42–55
- Panopoulos ST, Bournia VK, Trakada G, Giavri I, Kostopoulos Ch, Sfrikakis PP (2013) Mycophenolate versus cyclophosphamide for progressive interstitial lung disease associated with systemic sclerosis: a 2-year case control study. *Lung* 191:483–489
- Fischer A, Brown KK, Du Bois R, Frankel SK, Cosgrove GP, Fernandez-Perez ER, Huie TJ, Krishnamoorthy M, Meehan RT, Olson AL, Solomon JJ, Swigris JJ (2013) Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. *J Rheumatol* 40(5):640–646
- Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, Meehan RT, Brown KK (2006) Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. *Chest* 130:30–36
- Zamora AC, Wolter SPJ, Collard HR, Connolly MK, Elicher BM, Webb WR, King TE Jr, Golden JA (2008) Use of mycophenolate mofetil to treat scleroderma-associated interstitial lung disease. *Res Med* 102:150–155
- Raghu G, Collard HR, Anstrom KJ, Flaherty KR, Fleming TR, King TE Jr, Martinez FJ, Brown KK (2012) Idiopathic pulmonary fibrosis: clinically meaningful primary endpoints in phase 3 clinical trials. *Am J Respir Crit Care Med* 185(10):1044–1048
- Park JH, Kim DS, Park IN, Jang SJ, Kitaichi M, Nicholson AG, Colby TV (2007) Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtype. *Am J Respir Crit Care Med* 175:705–711
- Du Bois RM, Weycker D, Albera C et al (2011) Forced vital capacity in patients with idiopathic pulmonary fibrosis. Test properties and minimal clinically important difference. *Am J Respir Crit Care Med* 184:1339–1382
- Papiris SA, Manali ED, Kolilekas L, Kagouridis K, Triantafyllidou C, Tsangaris I, Roussos C (2010) Clinical review: idiopathic pulmonary fibrosis acute exacerbations: unravelling Ariadne’s thread. *Crit Care* 14(6):246
- Trang G, Steele R, Baron M, Hudson M (2012) Corticosteroids and the risk of scleroderma renal crisis: a systematic review. *Rheumatol Int* 32(3):645–653
- Katzenstein AL, Myers JL (2000) Nonspecific interstitial pneumonia and the other idiopathic interstitial pneumonias: classification and diagnostic criteria. *Am J Surg Pathol* 24(1):1–3
- Nagata N, Nagatomo H, Yoshii C, Nikaido Y, Kido M (1997) Features of idiopathic pulmonary fibrosis with organizing pneumonia. *Respiration* 64:331–335
- Wells AU, Steen V, Valentini G (2009) Pulmonary complications: one of the most challenging complications of systemic sclerosis. *Rheumatology* 48:iii40–iii44