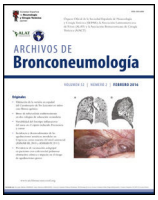
Arch Bronconeumol. 2018;54(11):549–550

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Biologics in the treatment of diffuse interstitial lung disease associated with connective tissue disease☆

Tratamiento biológico en la enfermedad pulmonar intersticial difusa asociada a las enfermedades del tejido conectivo

Tamara Alonso,[a] Santos Castañeda,[b] Julio Ancochea[a,*]

[a] Servicio de Neumología, Hospital Universitario La Princesa, Instituto de Investigación Sanitaria Princesa, Universidad Autónoma de Madrid (UAM), Madrid, Spain
[b] Servicio de Reumatología, Hospital Universitario La Princesa, Instituto de Investigación Sanitaria Princesa, Universidad Autónoma de Madrid (UAM), Madrid, Spain

Diffuse interstitial lung diseases (ILD) are a heterogeneous group of diseases of the pulmonary parenchyma that are classified as: idiopathic interstitial pneumonias; pneumonia associated with well-defined diseases, including connective tissue diseases (CTD); and primary ILD or those associated with other not well-defined diseases.[1]

The prevalence of diffuse ILD in CTD ranges from 5% to 80%, depending on the series and underlying disease.[2] A common denominator in its pathogenesis is pulmonary inflammation mediated by an immune mechanism, which also represents an important therapeutic objective. The development of diffuse ILD affects the morbidity and mortality of the associated underlying disease.[3] However, the scientific evidence available on the treatment of this entity is limited, and certain questions, such as type and time of treatment initiation, use of aggressive and/or combined therapy, the potential paradoxical effect of certain drugs, etc., have not been resolved.[4]

Until recently, treatment of ILD-CTD was based on glucocorticoids, despite the lack of controlled clinical trials to support the efficacy of such an approach. One retrospective study in a cohort of 71 patients with diffuse ILD associated with scleroderma (ILD-SCL) reports improvement in lung function in patients who received treatment for 1 year.[5]

Cyclophosphamide (Cx) is the most widely studied immunosuppressant (IS) therapy in ILD-CTD, and data are available from 2 multicenter clinical trials in ILD-SCL. The first, the Scleroderma Lung Study[6] in 158 patients randomized to receive Cx (2 mg/kg/day p.o.) or placebo, showed a significant improvement in forced vital capacity (FVC) after 1 year of treatment. The second study was performed in 45 patients who received low doses of prednisolone, 6 monthly infusions of Cx (600 mg/m^2), followed by azathioprine (2.5 mg/kg/day to a maximum of 200 mg/day), or triple placebo.[7] The results showed a non-significant improvement in FVC in the treatment group. The lack of more conclusive results may be due to the reluctance of investigators to include patients with progressive ILD-SCL receiving Cx in clinical practice.[4] In other ILD-CTDs, such as those associated with polymyositis, dermatomyositis, or mixed connective tissue disease (MCTD), retrospective case series show similar results.

Mycophenolate mofetil (MMF) is an immune modulator that reduces the proliferation of T and B lymphocytes, and its use as a corticosteroid-sparing agent has increased significantly in recent years. The use of MMF in ILD-CTD is based on retrospective studies, including a series of 125 patients with ILD-CTD (ILD-SCL, ILD associated with idiopathic inflammatory myopathies [ILD-IIM], and ILD associated with rheumatoid arthritis [ILD-RA]), which showed that it was well tolerated and allowed the effective reduction of the dose of glucocorticoids, achieving stabilization of lung function among the study patients.[8] In 2016, the results of the Scleroderma Lung Study II,[9] comparing MMF as first-line therapy with oral Cx in patients ILD-SCL, were published. The authors concluded that treatment with MMF for 2 years or with Cx for 1 year provided a significant improvement in lung function. MMF did not show superior efficacy to Cx, but its safety profile and tolerability were better, supporting its growing use.

Lung involvement often progresses despite treatment with IS, so other alternatives, such as biological therapy, must be sought. The use of biologics is contradictory, since despite their beneficial effect, they can promote the progression of lung disease in some cases.[10] Rituximab (RTX) is a monoclonal antibody (MaB) that reduces the number of B lymphocytes in peripheral blood over a 6–9 month period. It has shown evidence of efficacy in the depletion of B cells in various immune-mediated diseases, such as RA, vasculitis associated with antineutrophil cytoplasmic antibodies, and autoimmune thrombocytopenic purpura. Its potential efficacy in the treatment ILD-CTD has been analyzed in various studies, one of the most interesting of which was performed in a cohort of 50 patients with IS-resistant progressive fibrotic ILD (10 patients with ILD-IIM, 8 with ILD-SCL, 2 with ILD-RA, and 2 with ILD-MCTD), which showed

☆ Please cite this article as: Alonso T, Castañeda S, Ancochea J. Tratamiento biológico en la enfermedad pulmonar intersticial difusa asociada a las enfermedades del tejido conectivo. Arch Bronconeumol. 2018;54:549–550.

* Corresponding author.
E-mail address: j.ancochea@separ.es (J. Ancochea).

that RTX improved FVC after 6–12 months of treatment.[11] These preliminary results are expected to be confirmed in an ongoing clinical trial (RECITAL study NCT01862926) that is evaluating the efficacy of RTX compared to intravenous Cx in progressive ILD-CTDs.

Other biologics such as tocilizumab (anti-IL-6 MaB) might also be effective in the treatment of ILD-CTDs, although experience is limited to sporadic cases or small case series.[12] A recent study conducted in Spain with abatacept (a fusion protein that modulates T cell co-stimulation) in 63 patients with ILD-RA suggests that treatment with this drug may be effective in terms of clinical improvement and functional stabilization.[13] In contrast, anti-tumor necrosis factor (TNF) antibodies, such as infliximab and etanercept, must be used with caution, since they are associated with an increased risk of developing ILD in patients with RA and previous pulmonary involvement.[14,15] In the absence of controlled studies, we cannot be sure that this paradoxical effect is unique to the anti-TNF compounds, and this dilemma will only be resolved as experience is gained.

In summary, IS treatment is currently considered the backbone of ILD-CTD treatment, on the basis of retrospective studies and clinical trials conducted in ILD-SCL. The current therapeutic arsenal includes corticosteroids, azathioprine, MMF, and Cx. Some biologics, such as RTX, tocilizumab, and abatacept, are emerging as new options for severe, IS-refractory cases, although there are still many areas of uncertainty that call for caution in the generalized use of these products. Multicenter, randomized clinical trials are needed to clarify these aspects.

In conclusion, ILD-CTD constitute a group of complex, heterogeneous diseases in which, as in other fields of medicine, biomarkers, prognostic factors, and patient phenotypes must be defined in order to design more individualized treatments (personalized medicine). These new treatments might involve the use of combinations of drugs with different mechanisms of action. For these reasons, both research and real-world efforts must be united in a multidisciplinary collaboration among pulmonologists, radiologists, rheumatologists, and pathologists, so that we can achieve optimal goals in the assessment and treatment of these patients.

References

1. American Thoracic Society/European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2002;165:277–304.
2. Aparicio IJ, Lee JS. Connective tissue disease-associated interstitial lung diseases: unresolved issues. Semin Respir Crit Care Med. 2016;37:468–76.
3. Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet. 2012;380:689–98.
4. Maher TM. Inmunosupression for connective tissue disease-related pulmonary disease. Semin Respir Crit Care Med. 2014;35:265–73.
5. Ando K, Motojima S, Doi T, Nagaoka T, Kaneko N, Aoshima M, et al. Effect of glucocorticoid monotherapy on pulmonary function and survival in Japanese patients with scleroderma-related interstitial lung disease. Respir Investig. 2013;51:69–75.
6. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al., Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. N Eng J Med. 2006;354:2655–66.
7. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum. 2006;54:3962–70.
8. Fischer A, Brown KK, du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Pérez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol. 2013;40:640–6.
9. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophospamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4:708–19.
10. Pérez-Álvarez R, Pérez de Lis M, Díaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011;41:256–64.
11. Keir GJ, Maher TM, Ming D, Abdullah R, de Lauretis A, Wickremasinghe M, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology. 2013;9:353–9.
12. Manfredi A, Sebastiani M, Cassone G, Colaci M, Sandri G, Ferri C. Tocilizumab for the treatment of patients with rheumatoid arthritis and interstitial lung diseases: a case series. Clin Exp Rheumatol. 2018;36:342.
13. Fernández-Díaz C, Loricera J, Castañeda S, López-Mejías R, Ojeda-García C, Olivé A, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: a national multicenter study of 63 patients. Semin Arthritis Rheum. 2018, http://dx.doi.org/10.1016/j.semarthrit.2017.12.012, pii:S0049-0172(17)30636-4 (in press).
14. Jani M, Hirani N, Matteson EL, Dixon WG. The safety of biologic therapies in RA-associated interstitial lung disease. Nat Rev Rheumatol. 2014;10:284–94.
15. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum. 2014;43:613–26.