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EDITORIAL

Current therapeutic strategies in connective tissue disease-related interstitial lung disease: introduction to the special issue

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Abstract

This Editorial introduces the Special Issue on the efficacy and safety of current treatment strategies for patients with connective tissue disease-related interstitial lung disease, including the use of immunosuppressants, such as cyclophosphamide, mycophenolate mofetil and rituximab, and antifibrotic drugs.

Keywords: connective tissue diseases, cyclophosphamide, interstitial lung diseases, mycophenolate, nintedanib, pierfenidone, rituximab.

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Over the past two decades, increasing attention has been paid to interstitial lung involvement in patients with connective tissue diseases (CTDs), such as rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus, Sjogren's syndrome and idiopathic inflammatory myopathies (IIM), due to their negative impact on the quality of life and life expectancy of these patients. Major efforts have been made to define the genetic predisposition, pathophysiology, clinical behaviour and, ultimately, clinical progression of interstitial lung disease (ILD) among different CTDs. Several studies in the last years have also examined the long-term prognosis of CTD-ILDs in comparison to that of idiopathic pulmonary fibrosis (IPF), a progressive fatal ILD. In fact, despite CTD-ILD being usually characterized by a slow decline in lung function, a non-negligible proportion of patients develops an IPF-like 'progressive fibrotic phenotype' characterized by rapid functional decompensation, a lack of response to therapy and reduced survival.[1] The scenario is further compounded by the fact that the current management of CTD-ILD is mostly based on the results of observational studies and expert opinion, with high-level evidence from randomized clinical trials limited to the treatment of SSc-ILD.[2]

This special issue in *Drugs in Context* discusses the current knowledge regarding the available therapeutic armamentarium for CTD-ILD, including the use of immunosuppressants, such as cyclophosphamide, mycophenolate mofetil and rituximab, and antifibrotic drugs. Despite a number of biological drugs (e.g. anti-IL6, anti-TNFα, abatacept) having also been used in different CTD-ILD on the basis of their proven efficacy in the management of extra-pulmonary disease manifestations, convincing evidence about their efficacy is still lacking. Haemopoietic stem cell transplantation and lung transplantation have also proven to be effective in patients with refractory disease, especially in SSc-ILD, but their implementation is limited to specific Centres of Excellence.

Cyclophosphamide, an alkylating agent approved for the treatment of different haematological neoplasms and for bone marrow transplantation conditioning regimens, usually represents the first-line therapeutic approach in the management of severe CTD-ILD. As discussed in the systematic review by Nucera et al.,[3] there is high-level evidence supporting the use of cyclophosphamide in patients with progressive fibrotic SSc-ILD. By contrast, its benefit in patients with ILD related to other CTDs is variable. Moreover, there are a number of limitations to the use of cyclophosphamide related to its unsatisfactory safety profile, poor tolerability, and short-lasting effect on lung function.[3]

Mycophenolate, an anti-metabolite drug, is currently regarded as a therapeutic alternative to cyclophosphamide in

patients with progressive CTD-ILD. Cassone et al.[4] provide a comprehensive overview regarding the use of mycophenolate mofetil in SSc-ILD and other types of CTD-ILD. They argue that most of the current evidence is based on the results of three trials conducted in patients with SSc-ILD and that there is limited information from observational data in ILD secondary to IIM, systemic lupus erythematosus, and other CTDs. Additional randomized controlled clinical studies are strongly needed to define the efficacy and safety profile of mycophenolate mofetil in different patient subgroups according to the specific disease and clinical and radiological correlates.[4]

Rituximab, an anti-CD20 monoclonal antibody approved for use in patients with RA and anti-neutrophil cytoplasmic antibody-associated vasculitis, has been recently proposed as rescue therapy in patients with CTD-ILD refractory to treatment with cyclophosphamide and/or mycophenolate. Vacchi et al.[5] review the literature regarding the efficacy and safety of rituximab use in CTD-ILD. Although mostly based on observational studies, the available data suggest that the use of rituximab is associated with the stabilization of lung functional decline in severe progressive SSc-ILD and ILD related to RA and IIM. However, similar to cyclophosphamide and mycophenolate, there are some concerns related to the paucity of data from adequately powered clinical trials of rituximab and to the increased risk of serious adverse events (e.g. severe infections) in patients with CTD-ILD.

Finally, Erre et al.[6] discuss the current evidence regarding the efficacy and safety of pirfenidone and nintedanib, two antifibrotic drugs approved for use in patients with IPF, in the management of CTD-ILD. Experimental, preclinical, and clinical data are presented regarding the mechanisms involved in the antifibrotic potential of these drugs in patients with CTD-ILD. As discussed by Erre et al.,[6] nintedanib is currently licensed to reduce the decline of lung function in patients with SSc-ILD and other progressive fibrotic types of ILD. By contrast, in the context of limited available data, there is no evidence supporting the efficacy of pirfenidone in CTD-ILD. However, results from ongoing clinical trials are eagerly awaited to define the potential of nintedanib and pirfenidone in different subgroups of CTD-ILD according to specific disease and clinical phenotypes.

In summary, the articles published in this Special Issue provide a comprehensive and updated overview of the available pharmacological treatment options in patients with CTD-ILD, an area of clinical medicine that is likely to face significant developments over the next 5–10 years.

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References

1. Collins BF, Raghu G. Antifibrotic therapy for fibrotic lung disease beyond idiopathic pulmonary fibrosis. *Eur Respir Rev*. 2019;28(153). https://doi.org/10.1183/16000617.0022-2019
2. Erre GL, Sebastiani M, Fenu MA, et al. Efficacy, safety, and tolerability of treatments for systemic sclerosis-related interstitial lung disease: a systematic review and network meta-analysis. *J Clin Med*. 2020;9(8):2560. https://doi.org/10.3390/jcm9082560
3. Nucera V, Gerratana E, Giallanza M, La Corte L, Sangari D, Atzeni F. Efficacy of cyclophosphamide in treating connective tissue disease-related interstitial lung diseases. *Drugs Context* 2021;10:2020-9-1. https://doi.org/10.7573/dic.2020-9-1
4. Cassone G, Sebastiani M, Vacchi C, Erre GL, Salvarani C, Manfredi A. Efficacy and safety of mycophenolate mofetil in the treatment of rheumatic disease-related interstitial lung disease: a narrative review. *Drugs Context* 2021;10:2020-8-8. https://doi.org/10.7573/dic.2020-8-8
5. Vacchi C, Manfredi A, Cassone G, Erre GL, Salvarani C, Sebastiani M. Efficacy and safety of rituximab in the treatment of connective tissue disease-related interstitial lung disease. *Drugs Context* 2021;10:2020-8-7. https://doi.org/10.7573/dic.2020-8-7
6. Erre GL, Sebastiani M, Manfredi A, et al. Antifibrotic drugs in connective tissue diseaserelated interstitial lung disease (CTD-ILD): from mechanistic insights to therapeutic applications. *Drugs Context* 2021;10:2020-8-6. https://doi.org/10.7573/dic.2020-8-6