AIMS

To discuss the current knowledge on connective tissue disease associated interstitial lung disease.

SUMMARY

Connective tissue diseases (CTDs) are an important differential diagnosis in many pulmonary diseases and may present as nodules, pleural or bronchial diseases and as different patterns of interstitial lung diseases (ILD). Also, other differential diagnoses of dyspnea in ILD patients with CTD have to be analyses, i.e. pulmonary embolism, infection in often immunocompromised patients, drug related interstitial lung diseases and other manifestations, e.g. pulmonary hypertension. Therefore, a thorough clinical evaluation in the context of multidisciplinary diagnosis is necessary in the workup of interstitial lung diseases (ILD) in order to detect a connective tissue disease as cause of ILD. This includes the evaluation of auto-antibodies. Yet, false positive and negative values have to be taken into account. Moreover, while often considered as a single entity, "CTD-ILD" actually indicates a heterogeneous spectrum of CTDs and a variety of patterns in HRCT and histology [1]. In many of the CTDs, ILDs are associated with a significant morbidity and are often main causes of mortality in patients with CTD, e.g. in scleroderma [2, 3].

Yet, many patients with interstitial lung diseases have some clinical features suggesting an underlying autoimmune process but do not meet established criteria for CTDs. Recently, an ATS/ERS task force proposed a term "interstitial pneumonia with autoimmune features" (IPAF) offering classification criteria with the presence of a combination of features from clinical domains (i.a. specific extrathoracic features), a serologic domain (i.e. specific autoantibodies), and a pattern domain (i.e. HRCT and histopathological patterns, or pulmonary physiologic characters). IPAF should be used to identify individuals with features suggestive of, but not definitive for, a CTD and future research will have to establish further insights into this part of ILD patients [4].

Mainstay of therapy for all forms of CTD-ILDs are immunosuppressive drugs which should yet be reserved only for those patients with clinically significant and/or progressive disease. Moreover, in most CTDs, the management of CTD-ILD is still not evidence based, meaning that there is a desperate need for controlled trials for all CTD-ILDs. Furthermore, non-pharmacologic management strategies and treatment of comorbidities or aggravating factors should be part of a comprehensive treatment for patients with CTD-ILD [5].

With regards to therapy, most data are related to scleroderma. The scleroderma Lung Study I reported that patients with a one year treatment with cyclophosphamide in patients with scleroderma-associated ILD had a significant while modest beneficial effect on pulmonary function, dyspnea, thickening of the skin, and health-related quality of life which were maintained through the 24 months of the study [6, 7]. Another report on the use of mycophenolate mofitil in a large, diverse cohort of CTD-ILD patients showed that this drug was well tolerated and was associated with stable or even improved pulmonary function over a median of 2.5 years of follow-up [8]. Recently, the scleroderma...
lung study II was presented at various conferences. This study compared the effects of cyclophosphamide to MMF and reported that both cyclophosphamide and MMF are efficacious in treating progressive SSc-associated ILD with adverse effects with MMF [9]. As another alternative, the use of the CD20 antibody Rituximab is discussed and has been reported to be of value in some case series [10]. Currently, also the in IPF established antifibrotics are being investigated as potential drugs in the treatment of SSC-associated ILDs [11].

Still, potential side effects of the immunosuppressive drugs have to be taken into account and the timing, dosages, durations and which specific drugs to be used in specific CTD-ILDs have still to be established.

REFERENCES

1. Interstitial lung disease evaluation: detecting connective tissue disease. Fischer A, Lee JS, Cottin V. Respiration. 2015
3. Ph R Bauer et al. Influence of Interstitial Lung Disease on Outcome in Systemic Sclerosis-A population-Based Historical Cohort Study. CHEST 2013; 144(2):571–577
11. Khana et al., ERS 2015

EVALUATION

1. Which answer is correct?
   CTD-ILD is
   a. A rare differential diagnosis in ILD
   b. Is associated with a significant mortality
   c. Has a low morbidity
   d. Is easy to be diagnosed

Answer B

2. Which answer is incorrect?
   Treatment of CTD-ILD is...
   a. evidence based
   b. to be discussed only in progressive and/or significant disease
   c. associated with potential side effects as pulmonary infections
   d. also consisting of non-drug treatments

Answer A
3. **Which answer is correct?**
   a. IPAF is a new ILD entity
   b. Antifibrotics are licensed for the treatment of CTD-ILDs
   c. MMF has less side effects than cyclophosphamide
   d. Positive autoantibodies are 100% sensitive and specific for CTD-ILDs

Answer C