Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Association of anti-aminoacyl-transfer RNA synthetase antibody and anti-melanoma differentiation-associated gene 5 antibody with the therapeutic response of polymyositis/dermatomyositis-associated interstitial lung disease

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ARTICLE INFO

Article history:
Received 20 January 2016
Received in revised form
6 August 2016
Accepted 25 August 2016

Keywords:
Anti-aminoacyl-transfer RNA synthetase antibody
Anti-melanoma differentiation-associated gene 5 antibody
Interstitial lung disease
Polymyositis/dermatomyositis
Amyopathic dermatomyositis

ABSTRACT

Background: We attempted to clarify whether the presence of anti-aminoacyl-transfer RNA synthetase antibody (anti-ARS Ab) or anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab) is associated with the therapeutic response of polymyositis/dermatomyositis-associated interstitial lung disease (PM/DM-ILD).

Methods: We retrospectively investigated 22 patients with PM/DM-ILD (10 positive for anti-ARS Ab and nine positive for anti-MDA5 Ab) for whom antibody analysis of conserved serum was possible. We assessed mortality in the first three months as the therapeutic response in the acute phase and compared changes in clinical data for up to one year considered as the chronic phase. We classified the clinical changes over the year into three groups: Improvement (increased % vital capacity [%VC] or diffusing capacity of the lung for carbon monoxide [$\%D_{LCO}$] ≥ 10 or 15%), deterioration (decreased %VC or $\%D_{LCO}$ ≥ 10 or 15%), and no change (remainder of the changes). The extent of abnormality demonstrated by high-resolution computed tomography (HRCT) was scored.

Results: Positivity for anti-MDA5 Ab, but not for anti-ARS Ab, was associated with mortality in the first 3 months. Evaluation of the therapeutic response in the first year showed that positivity for the anti-ARS Ab, but not for the anti-MDA5 Ab, was associated with an improvement in $\%D_{LCO}$ and a decline in the serum KL-6 levels. Positivity for the anti-ARS Ab or negativity for anti-MDA5 Ab was associated with a greater decrease in bronchial dilatation as seen by HRCT.

Conclusions: Anti-ARS and anti-MDA5 Abs are associated with the therapeutic response of PM/DM-ILD.

http://dx.doi.org/10.1016/j.resinv.2016.08.007
2212-5345/

Please cite this article as: Yoshida N, et al. Association of anti-aminoacyl-transfer RNA synthetase antibody and anti-melanoma differentiation-associated gene 5 antibody with the therapeutic response of polymyositis/dermatomyositis-associated interstitial lung disease. Respiratory Investigation (2016), http://dx.doi.org/10.1016/j.resinv.2016.08.007

1. Introduction

Interstitial lung disease (ILD), a pivotal organ involvement in patients with polymyositis/dermatomyositis (PM/DM), occurs in approximately 50% of cases and is a significant cause of mortality [1,2]. Anti-aminoacyl-transfer RNA synthetase antibody (anti-ARS Ab) has been identified in PM/DM patients [3]. This class of autoantibody includes anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, and anti-KS antibodies. Anti-ARS-positive patients are defined as having antisynthetase syndrome (ASS) and show homogeneous clinical features, such as those complicating ILD [4,5].

A subtype of PM/DM patients with definite cutaneous manifestations of DM, and without clinically significant muscle involvement, are defined as having amyopathic dermatomyositis (ADM). It has been reported that patients with ADM have a significantly high risk of developing rapidly progressive ILD (RP-ILD), which is associated with a poor therapeutic response [6–8]. The clinical course of RP-ILD complicated by ADM is fatal [7]. The anti-clinically ADM (CADM) 140 Ab was first identified by Sato et al. [6]. The autoantigen recognized by the anti-CADM140 Ab was later identified as RNA helicase, which is encoded by melanoma differentiation-associated gene 5 (MDA5) [8]. The presence of anti-MDA5 Ab is associated with fatal RP-ILD in PM/DM patients [6–9].

The purpose of the present study was to clarify whether the presence of anti-ARS or anti-MDA5 Ab is associated with the therapeutic response of PM/DM-associated ILD (PM/DM-ILD) patients.

2. Materials and methods

2.1. Study subjects

The characteristics and clinical courses of PM/DM-ILD patients are shown in Table 1. We analyzed 22 patients with PM/DM-ILD (8 males, 52.5 [49.8–60.3] years old), including 10 anti-ARS-positive patients and nine anti-MDA5-positive patients. The patients had been consecutively monitored from 2002 to 2013 at our hospitals, and their serum was collected before the start of therapy for analysis of anti-ARS and anti-MDA5 Ab levels. Patients fulfilled the American Rheumatism Association preliminary criteria for PM/DM [10]. The diagnosis of ADM was based on the diagnostic criteria proposed by Sontheimer [11], i.e., DM patients who had not developed clinical muscle symptoms or serum muscle enzyme abnormalities for more than six months after onset of skin manifestations. Similarly, patients with no clinical evidence of muscle disease but with subclinical evidence of myositis on laboratory, electrophysiological, and/or radiologic evaluation were defined as having hypomyopathic DM (HDM). Patients with ADM or HDM were considered to have CADM. Two respirologists diagnosed patients with ILD on the basis of high-resolution computed tomography (HRCT) and clinical findings. Baseline serum KL-6 levels and pulmonary function were analyzed at the start of therapy. Follow-up pulmonary function and serum KL-6 levels were measured one year after the start of therapy. Other diseases, such as infectious and malignant disease, were excluded. None of the patients had undergone surgical lung biopsy. Patients with acute onset of ILD were defined as those presenting with progressive dyspnea and showing abnormal opacities on chest radiograph within one month after onset of respiratory symptoms. We set the endpoint for evaluation of the therapeutic response in the acute phase as mortality within three months after the start of therapy, as previously reported [12]. Similarly, we set the endpoints for the chronic phase as changes in pulmonary function and serum KL-6 levels over the year. We classified the clinical changes over one year into three groups: Improvement (increase of % vital capacity [%VC] or diffusing lung capacity for carbon monoxide [$\%D_{LCO}$] $\geq$ 10% or 15%), deterioration (decreased %VC or $\%D_{LCO} \geq$ 10% or 15%), and no change (remainder of the changes) according to the global official guideline of idiopathic pulmonary fibrosis [13]. We observed the study subjects for up to one year after the start of therapy, and none of the patients withdrew from the study.

We received approval from the Institutional Review Board of Kurume University in accordance with the ethical standards of the Helsinki Declaration of 2008 (Approval date: August 2, 2008 and March 3, 2011; Approval number: 08067 and 10289, respectively). Written informed consent was obtained from all patients.

2.2. Interpretation of HRCT images and scores

HRCT images prior to treatment ("baseline HRCT") for 22 patients and follow-up HRCT images for 20 patients were analyzed (median interval 273.0 [range, 15–583] days after the start of therapy). The protocol consisted of end-inspiration in the supine position, and 0.5- to 1.5-mm collimation sections reconstructed with a high-spatial-frequency algorithm at 1 or 2 cm intervals. Images were interpreted at a window setting appropriate for viewing the lung parenchyma (window level, −600 to −700 Hounsfield units [HU]; window width, 1200–1500 HU), as previously reported [14].

Abbreviations: ILD, Interstitial lung disease; PM/DM, polymyositis/dermatomyositis; Anti-ARS Ab, Anti-aminoacyl-transfer RNA synthetase antibody; ASS, antisynthetase syndrome; Anti-MDA5 Ab, melanoma differentiation-associated gene 5 antibody; CsA, cyclosporin A; IVCY, intravenous cyclophosphamide

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