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Review

Personalized medicine for connective tissue disease: Historical and future perspectives

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ABSTRACT

Connective tissue disease (CTD), previously termed collagen disease, is a group of disorders, characterized by rheumatic symptoms, autoimmunity, and degeneration of the pathohistology of the extracellular matrix. Better classification and disease subsetting, as well as introduction of immunosuppressants and molecular-targeting drugs, have much improved patients' quality of life and prognosis. The treat-to-target strategy in combination with emphasis on early diagnosis and intervention is now advocated for many CTDs. However, there remains a need to determine the appropriate management for individual patients, as clinical presentation and treatment response are highly variable among patients. A personalized medicine approach based on comprehensive patient profiles can improve patient care and long-term outcomes by decreasing the number of treatment failures, improving drug safety, and reducing the complications and organ damage associated with the disease and its treatment. Tremendous efforts have been made to identify patients who require early aggressive treatment, but the current knowledge on predicting the treatment response to individual drugs is limited. Better coordination between basic and clinical science is the key to providing a basis for tailored approaches for individual patients with CTD.

1. Introduction

Connective tissue disease (CTD), previously termed collagen disease or collagen vascular disease, is a group of disorders, characterized by rheumatic symptoms, autoimmunity, and histopathological features of degeneration or damage of extracellular matrix proteins. This disease currently includes rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis or dermatomyositis (PM/DM), Sjögren's syndrome (SS), various types of vasculitides, and related disorders. Several epidemiological studies and genome-wide gene association studies have revealed that CTD is a complex polygenic disease, which results from a combination of a number of genetic polymorphisms and environmental triggers. The pathogenic process of CTD might lead to end-stage failure of various organ systems, including the heart, lungs, and kidneys, and shorten patients' life span, if it is managed inadequately. Glucocorticoids (GCs) were the only treatment option for patients with CTD for many years previously, but medical advances have increased the number of treatment options, such as immunosuppressants and molecular-targeting biologics and small molecules, resulting in improvement of long-term prognosis. However, there remains a need to determine the appropriate management for individual patients, since clinical presentation and the treatment response are highly variable among patients, even in those with the same diagnosis. In addition, the risks for severe adverse effects of treatment regimens vary among patients. Personalized or precision medicine based on comprehensive patient profiles can improve the patient care and long-term outcomes by decreasing the number of treatment failures, improving drug safety, and reducing the complications and organ damage associated with the disease and its treatment.

Personalized medicine has the potential to tailor therapy with the best response and highest safety margin to ensure better patient management. By enabling each patient to receive earlier diagnosis, risk assessment, and optimal treatment, personalized medicine holds the promise for improving health care, while also lowering the costs. However, there is little implementation of

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personalized medicine in the CTD field at this moment. This review focuses on the history and current standings of CTD management, as well as on potential prospects for future implementation of personalized medicine.

2. The disease concept of CTD

It had long been believed that diseases reside in certain organs of the human body and every diagnostic endeavor was directed toward establishing the fundamental organ disease. Paul Klemperer and colleagues challenged this prejudice on the basis of careful observations of a huge number of postmortem histopathological samples. He proposed the term “diffuse collagen disease” for a group of conditions that affect multiple organ systems with heterogeneous clinical and anatomical involvement, based on a common morphologic feature: systemic alteration of connective tissue components, mainly collagens, specifically of its intercellular components [1]. The disease category initially included SLE and SSc, but has been later expanded [2]. This landmark article significantly contributed to establishment of a new disease concept independent of the organ, but the “collagen disease” was later replaced by the term “CTD,” because connective tissue is a more broad and general term expressing the main affected site of the disease [3]. Connective tissue is the main component of the extracellular matrix that binds together and supports the organ structure. This tissue forms a framework for the body, and is composed of two major structural protein molecules: various types of collagens and elastin. Therefore, CTDs usually involve such body structures as the skin, muscles, and joints, but can also affect virtually all organ systems, including the eyes, heart, lungs, kidneys, gastrointestinal tract, and blood vessels. In the broad sense, CTDs also include heritable disorders of the connective tissue, such as Ehlers-Danlos syndrome, but CTDs, previously termed collagen disease, are characterized by concomitant autoimmunity and inflammation, which cause degeneration and destruction of connective tissue. Currently, CTDs cover a variety of diseases listed in Table 1.

3. Disease classification and subsetting of CTDs

CTDs are multisystem disorders with poorly understood etiology; they are heterogeneous in their presentation, course, and outcome, and do not have a single clinical, laboratory, pathologic, or radiologic feature that could serve as a “gold standard” to support their diagnosis. In clinical practice, CTDs are diagnosed primarily based on characteristic clinical and histopathological findings,

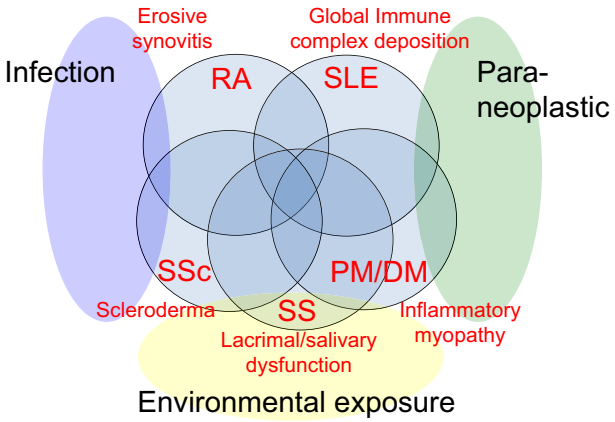

Fig. 1. Uncertainty of diagnosis of connective tissue disease (CTD). Clinical diagnosis of CTD relies on characteristic clinical and histopathological findings, which often discriminate one disease from the others (shown in red). However, many patients do not present typical clinical and histopathological features, and some patients even show two or more overlapping features of CTDs. In addition, there are several mimics, which are induced by infection, neoplasm, or environmental exposures. DM: dermatomyositis, PM: polymyositis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, SSc: systemic sclerosis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

which often discriminate one disease from other CTDs. For example, symmetrical erosive synovitis is indicative of the RA diagnosis, while skin sclerosis of fingers expanding to proximal parts of the body, such as forearm, upper arm, and trunk, is highly specific to SSc. It is quite useful to make diagnosis in clinical practice, since it enables us to predict future clinical course, treatment response, and prognosis in individual patients. However, many patients who do not have typical clinical or histopathological features, while some patients even have two or more overlapping features of CTDs (Fig. 1). In addition, there are several mimics, which are induced by infection, neoplasm, and environmental exposures, such as toxins and drugs. Because of CTDs complexity, their diagnosis is challenging and is often made by experts by means of comprehensive evaluations based on numerous clinical experiences. The majority of CTDs have classification criteria, which are aimed at identifying well-defined, relatively homogeneous groups of patients for clinical research and clinical trial purposes across different regions. Classification criteria are not intended to use for making diagnosis of individual patients in clinical setting,

Table 1
Major connective tissue diseases and estimated number of patients in Japan.

	Estimated number of patients in Japan[a]
Rheumatoid arthritis (RA)	7,00,000−1,000,000[b]
Systemic lupus erythematosus (SLE)	62,988
Systemic sclerosis (SSc)	30,786
Polymyositis/dermatomyositis (PM/DM)	21,031
Mixed connective tissue disease (MCTD)	10,811
Sjogren's syndrome (SS)	9111[c]
Polyarteritis nodosum (PN)	3442
Microscopic polyangiitis (MPA)	8551
Granulomatosis with polyangiitis (GPA)	2534
Eosinophilic granulomatosis with polyangiitis (EGPA)	1356
Giant cell arteritis (GCA)	199[c]
Takayasu's arteritis (TA)	6119

[a] Based on the number of patients registered in the Intractable Disease Program sponsored by Japanese Ministry of Health, Labour and Welfare in 2017.
[b] Estimation by Japanese Ministry of Health, Labour and Welfare.
[c] The number of patients appears underestimated because registration of the Intractable Disease Program sponsored by Japanese Ministry of Health, Labour and Welfare has just started in 2016.

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