EXHIBIT 14

"Epidemiology of Connective Tissue Disorders"

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Epidemiology of connective tissue disorders

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The reported prevalence and incidence of connective tissue disorders are quite variable, depending on differences in study methodology. Most important differences are the study duration, the classification criteria used for diagnosis and the country in which the study was undertaken. Sjögren's syndrome has the highest prevalence ranging between 0.5 and 3% of a given population. The prevalence of systemic lupus erythematosus (SLE) is estimated between 15 and 50 per 100 000 individuals, with a female:male ratio of 6–10:1 in the age group between 15 and 40 yrs. The prevalence of systemic sclerosis is lower, however, varying significantly between different studies and countries. The prevalence of overlap syndromes, especially mixed connective tissue disease, is unknown, and polymyositis and dermatomyositis are regarded as very rare rheumatic diseases.

Though the classification criteria for the connective tissue disorders have not been developed for the purpose of diagnosing an individual patient, these criteria still are the most valuable tool for the identification of patients with systemic rheumatic diseases such as connective tissue disorders.

Systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome (SS), inflammatory muscle diseases and overlap-syndromes are grouped together as connective-tissue disorders. Though specific clinical and pathophysiological symptoms and mechanisms for the different diseases from this group have been detected, numerous overlapping features (sustained inflammation, autoimmune processes with the development of specific autoantibodies and the systemic clinical phenotype involving several organs) still justify the classification as a group of connective tissue diseases [1]. Due to this diversity of clinical symptoms, the variable course of the disease diagnosis is still challenging and, as outlined below, epidemiological data difficult to determine.

Systemic lupus erythematosus

SLE is a prototypic autoimmune disease with a diverse array of clinical manifestations. It is one of the most common autoimmune disorders in women during their childbearing years. Peak incidence occurs between the age of 15 and 40 yrs, with a female:male ratio of 6–10:1. Age at onset of disease can range from infancy to advanced age, however. In pediatric and older-onset patients, the female:male ratio is ~2:1. In the USA, the average incidence of SLE has been estimated to range between 1.8 and 7.6 cases per 100 000 person-years [2]. Incidence rates in Europe are similar, ranging from 3.3 to 4.8 per 100 000 person-years. The incidence of SLE is greater in Afro-Americans compared with Caucasians [3]. SLE shows a much higher frequency among first degree relatives of patients; it appears in ~25–50% of monozygotic twins.

The prevalence of SLE in the USA ranges from 15 to 50 per 100 000 persons. SLE is diagnosed worldwide with similar incidences as those reported in the USA.

Sjögren's syndrome

SS is a slowly progressive, inflammatory autoimmune disease affecting primarily the exocrine glands. Diagnostic hallmarks are diminished tear production, xerostomia and presence of autoantibodies, especially Ro (SS-A) and La (SS-B) antibodies. Differences in classification criteria (accepting only clinical symptoms of Sicca syndrome for diagnosis or postulating also serological parameters of autoimmunity, especially Ro and La-antibodies) may complicate the interpretation of epidemiologic data.

SS can occur at all ages, but it affects primarily females during the fourth and fifth decades of life. SS frequency appears to increase with age, with a prevalence of about 3% in people above an age of 50 yrs [4]. The female:male ratio is about 9:1.

Systemic sclerosis

SSc, also termed scleroderma, is a multisystem disease characterized by structural and functional abnormalities of small blood vessels, fibrosis of the skin and internal organs, activation of the immune system and autoimmunity. The published incidence rates in the USA [5] and European countries range between 4.5 and 18.7 new cases per million. The recently reported prevalence in the USA (260 per million) [6] appears to be higher than in other countries (13–48 per million in the UK [7]; 86 per million in Australia [8]. However, another prospective study from Estonia revealed out a prevalence of around 2280 per million, perhaps due to a less stringent definition of 'scleroderma spectrum disorders' [9]. These numbers are so different from other reports that comparability of inclusion criteria is doubtful. Overall, there does not appear to be a difference between countries with cold or warm climates or different regions within a single country.

Age of onset is most commonly in the range of 30–50 yrs. SSc is uncommon in children younger than 13 yrs. In first degree relatives the prevalence is significantly higher than in the general population: 1.6 *vs* 0.026% [6]. Like other connective tissue disorders, SSc is also predominant in females with ratios of women to men between 5 and 14:1. Ethnic

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backgrounds influence survival and disease manifestation. Progressive pulmonary interstitial fibrosis occurs less frequently in Caucasian patients, when compared with Afro-American and Japanese patients. Environmental agents have been implicated in the development of SSc. Silica dust, frank silicosis and exposure to organic solvents, vinyl chloride or L-tryptophan significantly increase the risk of SSc or other fibrosing illnesses.

Polymyositis and dermatomyositis

Criteria for the classification of patients with polymyositis and dermatomyositis include symmetric muscle weakness, evidence of myositis proven by muscle biopsy, increase in serum skeletal muscle enzymes, characteristic electromyographic pattern and, in case of dermatomyositis, typical rash. The overall annual incidence of polymyositis–dermatomyositis ranges from 2 to 10 new cases per million persons in different populations [10]. There is a trend towards increasing incidence in several communities [11]. Inflammatory myopathy can occur at any age; however, there is a bimodal distribution with peaks between age 10 and 15 yrs in children and between 45 and 60 yrs in adults. Myositis associated with malignancy and inclusion body myositis are common after the age of 50 yrs. The female:male ratio is about 2.5:1; however, inclusion body myositis appears to be more frequent in men. Inflammatory myositis is most common in Afro-Americans.

Overlap syndromes

Overlap syndromes are defined by a combination of major features of more than one rheumatic disease present in the same patient and often defined by a specific serological test. Raynaud's phenomenon, arthritis and sclerodactyly are common features, polymyositis and fibrosing alveolitis more serious manifestations.

Due to the diversity of clinical appearance, there exist no reliable estimates addressing the prevalence of overlap syndromes [12]. In general, patients with an overlap syndrome appear to occur less frequent than patients with SLE, but more frequent than patients with SSc or inflammatory myopathy.

Mixed connective tissue disease (MCTD) a special form of overlap syndrome, first described by Sharp, has been subject of debate till today. Many authors do not regard MCTD as a distinctive disease entity; reliable data concerning its prevalence are not available.

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Rheumatology	Key messages
	• Connective tissue diseases are rare, but potentially life-threatening diseases. • They occur at all ages, but have a higher prevalence in young adults. • In most entities, women are affected significantly more frequent. • Incidence and prevalence vary among different racial/ethnical groups. • The spectrum of clinical manifestations is wide, often including mucocutaneous symptoms, arthritis/arthralgia and involvement of kidneys and lungs. • Laboratory evaluation shows signs of inflammation and markers of autoimmunity. • Classification criteria do not allow to diagnose all patients correctly but are helpful clinical instruments.

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