Best Practice & Research Clinical Rheumatology 30 (2016) 81–94

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

6

Cardiovascular risk and its modification in patients with connective tissue diseases

Miriam O'Sullivan [a, b, 1, 2], Ian N. Bruce [a, b, 1], Deborah P.M. Symmons [a, b, *]

[a] Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, UK
[b] NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Keywords:
Connective tissue diseases
SLE
Systemic sclerosis
Primary Sjögren's syndrome
Idiopathic inflammatory myopathies
Cardiovascular disease
Cardiovascular risk management

A B S T R A C T

It is well documented that patients with systemic lupus erythematosus (SLE) are at an increased risk of atherosclerotic cardiovascular (CV) disease. There is evidence that traditional risk factors and disease-related factors are involved in this increased risk. Less is known about CV risk and outcomes in other connective tissue diseases (CTDs). Future longitudinal observational studies may help to answer these important questions; however, because CTDs are rare, collaboration between clinicians with similar research interests is needed to ensure sufficiently large cohorts are available to address these issues.

Here, we review the evidence available for CV risk in CTDs and discuss the benefits of longitudinal observational studies in identifying CV outcomes. Structured care protocols for the management of CV risk in CTDs are lacking. We propose a target-based approach to assessing and managing CV risk in CTDs.

* Corresponding author. NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK. Tel.: +44 161 275 5044; fax: +44 161 275 5043.
E-mail address: Deborah.symmons@manchester.ac.uk (D.P.M. Symmons).
[1] Tel.: +44 161 275 5044; fax: +44 161 275 5043.
[2] Future address: Sligo University Hospital, Sligo, Ireland.

http://dx.doi.org/10.1016/j.berh.2016.03.003
1521-6942/

Introduction

Patients with inflammatory musculoskeletal diseases are at an excess risk of atherosclerotic cardiovascular disease (ACVD) compared to the general population. A meta-analysis of 24 mortality studies in patients with rheumatoid arthritis (RA) reported a weighted combined all-cause standardised mortality ratio (meta-SMR) of 1.50 (95% 1.39–1.61) with similar increases for ischaemic heart disease (meta-SMR 1.59; 95% CI 1.46–1.73) and stroke (meta-SMR 1.52; 95% CI 1.40–1.67) [1]. The bimodal pattern of death associated with systemic lupus erythematosus (SLE) was first described in 1976 [2], with the first mortality peak (within 1 year of diagnosis) being mainly due to active lupus and infection and the second peak (>5 years from diagnosis) being mainly due to cardiovascular events (CVEs). In 1997, Manzi et al. reported that the risk of myocardial infarction (MI) was >50 times higher in women aged 35–44 in the University of Pittsburgh lupus cohort than in age-matched women from the Framingham Offspring cohort [3].

In this chapter, we summarise the most recent studies on the risk of ACVD and the risk factors for ACVD in patients with SLE, systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIMs), mixed connective tissue disease (CTD) and primary Sjögren's syndrome (pSS). We performed a Medline search up until 30 November 2015 searching for 'cardiovascular risk' and 'cardiovascular mortality' and combined each with 'systemic lupus erythematosus', 'systemic sclerosis', 'Sjogren's syndrome', 'idiopathic inflammatory myopathy' and 'mixed connective tissue disease'. We have focussed on reporting relevant systematic reviews and papers published in the last 5 years.

We highlight the importance of longitudinal observational studies (LOSs) in contributing to this knowledge and on the value of embedding research in routine clinical practice. Finally, we review strategies for cardiovascular (CV) risk management in patients with CTDs.

CV disease in patients with SLE

SLE is a chronic inflammatory autoimmune condition with significant morbidity and mortality. The survival rates for SLE have improved significantly in recent years [4]. In an international study of 9547 patients from 23 centres, the all-cause SMR estimates decreased significantly between the 1970s and 2001. However, the CV SMR increased slightly [5]. CVEs remain one of the main causes of death in SLE.

CV mortality in patients with SLE

CV mortality is increased in SLE patients compared to the general population. In a meta-analysis of 27,123 SLE patients from 12 studies published before 2011, a threefold increased risk of all-cause mortality (meta-SMR 2.98, 95% CI 2.32–3.83) and an increased risk of death from cardiovascular disease (CVD) (meta-SMR 2.72, 95% CI 2.32–3.83) were noted [6]. None of the studies of mortality published since 2011 has had sufficient numbers of deaths to be able to report a CV-specific SMR [7,8]. The most recent study followed 2740 incident cases of SLE identified using the UK primary-care-based Clinical Practice Research Datalink and then linked to the national death register [9]. The mortality rate ratio compared to age-, sex- and practice-matched controls was 1.67 (95%CI 1.43, 1.94). Another UK-based study followed up an inception cohort of 382 SLE patients recruited from 1989 to 2010. The all-cause SMR was 2.0 (95% CI 1.5, 2.8), with CVEs being one of the most common causes of death (27%) [10].

Ethnicity may play a role in the risk of CV mortality in SLE. A systematic review of five observational studies involving 4469 Chinese patients with SLE found lower rates of death from CV causes than has been documented in other ethnic groups [11]. CVEs accounted for 11.5% of all deaths, whereas deaths from infection accounted for 33% of all deaths.

Traditionally, mortality studies have focussed on the underlying cause of death as recorded in the death certificate. A new methodology called multiple-cause-of-death analysis enables all the diagnoses recorded on the death certificate to be analysed. Two recently published studies have used this methodology in SLE. One study included 4815 death certificates from Sao Paulo, Brazil, on which SLE was listed as a cause of death between 1985 and 2005 [12]. The most common contributory causes of death were renal failure and sepsis. Only in 2003–2007, and in individuals aged <50 years when they