Human Immunology 78 (2017) 574–581

Contents lists available at ScienceDirect

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

Cytokine balance and behavioral intervention; findings from the Peer Approaches to Lupus Self-Management (PALS) project

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ARTICLE INFO

Article history:
Received 31 March 2017
Revised 26 June 2017
Accepted 10 July 2017
Available online 14 July 2017

Keywords:
Cytokines
Behavioral intervention
African American
Women
Systemic Lupus Erythematosus

ABSTRACT

The Peer Approaches to Lupus Self-Management program sought to address the disparate impact of systemic lupus erythematosus (SLE) on African American women through a peer mentoring intervention with aims of reducing stress, anxiety, and depression. Given the association between psychological health and immune function this study examines the relationship between patient reported outcomes (PROs) in these domains and immunologic indicators of disease activity. Twenty-three African American women with SLE served as mentees in the intervention from whom PRO measures were collected at the outset, midpoint, and end of the 12 week pilot study. Blood samples were collected pre- and post-intervention. Plasma was collected from the samples and cryopreserved for subsequent analyses. The strongest correlations were between the Generalized Anxiety Disorder measure and Th1/Th2 cytokine balance. Weaker correlations existed between depression and the Th1/Th2 cytokine balance. Assessment of fresh versus cryopreserved samples revealed that changes in Th1/Th2 cytokine balance within the intervention were generally equivalent, regardless of sample type. The PALS intervention resulted in significant improvements to anxiety and depression levels which were significantly associated with positive changes in Th1/Th2 cytokine balance indicating a possible underlying mechanism of action. The nature of this relationship warrants further study.

1. Introduction

Systemic Lupus Erythematosus (SLE or lupus) is a chronic autoimmune disease with acute periodic flare-ups of symptoms impacting any organ system and resulting in potentially life-threatening complications [1,2]. Other significant complications of treatment include weight gain, osteoporosis, osteonecrosis, accelerated atherosclerosis, and retinal damage [1–3]. Symptoms and side effects and complications can lead to significant functional and emotional challenges [4–7]. Patients often experience a high degree of psychological symptoms, including anxiety, depression, mood disorders, and decreased health-related quality of life [8–20].

Lupus disproportionately affects women and nonwhites [21,22]. Racial and ethnic minorities, the poor, and those lacking medical insurance and education are at highest risk for the preva-

Abbreviations: SLE, Systemic Lupus Erythematosus; PALS, Peer Approaches to Lupus Self-Management; PROs, patient reported outcomes; MCRC, Multidisciplinary Clinical Research Center; MUSC, Medical University of South Carolina; CDMP, Chronic Disease Self-Management Program; ASMP, Arthritis Self-Management Program; SLESH, Systemic Lupus Erythematosus Self-Help; ACR, American College of Rheumatology; LUP-QOL, Lupus Quality of Life measure; MOS, Medical Outcomes Study; SF-36, Short Form 36 Health Survey; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; PHQ, Patient Health Questionnaire; GAD, General Anxiety Disorder; PSS, perceived stress scale; PAM, Patient Activation Measure; EMRs, electronic medical records; CDW, clinical data warehouse; SLAM, Systemic Lupus Activity Measure; SLAQ, Systemic Lupus Activity Questionnaire; PGA, Patient Global Assessment; NRS, Numerical Rating Scale; PMA, phorbol myristate acetate.

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http://dx.doi.org/10.1016/j.humimm.2017.07.005
0198-8859/

lence, morbidity, and mortality associated with lupus [21,23–25]. Thus, the Peer Approaches to Lupus Self-Management (PALS) program was developed for African American women, as a culturally tailored peer mentoring intervention to help address the disparate impact SLE can have on this vulnerable population. In studies of predominantly low income and minority populations, peer mentors have been shown to help support healthy behaviors along with improved medication adherence and blood glucose monitoring in people with diabetes [26–39]. Additionally, there is some evidence that peer mentoring has also led to improvements in positive affect, sleep, social coping, and perception of bodily pain in rheumatic conditions [40,41]. Thus SLE is an optimal condition within which to test the effectiveness of the peer mentoring approach due to its high burden in African American women. To determine the effectiveness of the PALS intervention on the mentees, validated patient reported outcomes (PROs) were assessed.

Humoral autoimmunity in SLE is typically characterized as a Th2 dominant disease, likely in part due to reduced function or activity of regulatory T cell components [42]. Previous studies have assessed the relationships between stress, social support, and anxiety with immune function [43]. These studies have shown that high levels of psychological stress (including anxiety, worry and depression) are associated with altered regulatory T cell numbers and an altered Th1/Th2 balance (decreased IFNg and/or increased IL4) [44–46]. There is also evidence in scientific literature that links chronic stress and SLE disease activity [43]. The consensus of these studies has determined that long term stress, low levels of social support, and high levels of anxiety can lead to immune dysregulation and reduced function [47,48]. While the action of social support is not fully understood, it has been shown that stress and anxiety can alter the expression of genes vital in immune response [47,48]. Several Given the connection between stress and immune function, the suspected mechanism of action for this particular behavioral intervention is that it reduces stress and other associated psychosocial factors and in turn, positively impacts immune function. For this reason, there may be a relationship between the PROs associated with anxiety, worry, and depression and immunologic evidence of disease risk/activity. To ensure measurement of several relevant outcomes, PRO's assessed in the present study included disease self-management, measured with the Patient Activation Measure (PAM); health related quality of life (HRQOL), measured by the Lupus Quality of Life (LUP-QOL) questionnaire; and self-reported disease activity, measured with the Systemic Lupus Activity Questionnaire (SLAQ); along with standardized measures of stress (PSS), anxiety (GAD-7), and depression (PHQ-9). Determining an association of a particular PRO with biological processes might suggest that particular outcome is worth studying and using as an endpoint to refine the intervention and monitor its effect in patients.

The hypothesis is that such interventions will change behavior, which will lead to changes in health. However, there is a gap in the literature regarding whether there is an actual biologic mechanism (i.e., physiological changes to the immune expression of Th1/Th2 cytokine balance) that might lead to change in disease condition as well. Therefore, the primary aim of this study was to determine the effect of the PALS peer mentoring intervention on T cell immune function the relationship between PROs and immune profiles associated with disease activity as determined by blood Th1/Th2 cytokine imbalance to suggest such a mechanism. The second aim of this study was to validate our collection, storage, and analysis protocols in order to inform other trials as to the value and limitations of using cryopreserved mononuclear cell samples to determine these profiles.

2. Materials and methods

2.1. Intervention

The Peer Approaches to Lupus Self-Management (PALS) study was a single arm, pre-post pilot in which African American women with lupus were recruited from the Medical University of South Carolina (MUSC) P60 Multidisciplinary Clinical Research Center (MCRC) longitudinal cohort who consented to contact about research and through physician referral. The peer mentoring intervention (patients were matched with peer mentors who were considered competent in the management of their condition to provide modeling and reinforcement to participants) occurred by telephone for approximately 60 min every week for 12 weeks. Weekly content was adapted from the six modules of the Chronic Disease Self-Management Program (CDMP), Arthritis Self-Management Program (ASMP), and Systemic Lupus Erythematosus Self-Help (SLESH) Course [49–53], and further tailored to African American women with six added sessions based on cultural issues reported as important to African Americans in earlier research conducted by the principle investigator [54–56].

2.2. Participants

All participants were selected from a longitudinal observational web-based SLE database at the Medical University of South Carolina (MUSC), and these patients are seen on a regular basis in the MUSC lupus clinics. All participants meet at least four components of the 1997 American College of Rheumatology (ACR) revised criteria for SLE and have disease activity information available, as well as quality of life measures obtained in the database questionnaire [57]. This study was approved by the Medical University of South Carolina's IRB and written informed consent was obtained from all participants prior to study enrollment. As part of the informed consent process, participants agree to future re-contact regarding other research studies.

2.3. Data collection

Since this was a pilot investigation to obtain preliminary results that could inform development of a larger study, our goal was to assess changes in SLE patients; not differences between patients and controls. Therefore, we adopted a pre/post study design within which participants served as their own control. Primary outcomes of the study included PROs as well as Th1/Th2 balance in peripheral blood mononuclear cells. Study questionnaires were carefully chosen based on available evidence and in order to measure key elements of the study aims. The primary method of data collection was face to face interview. Mentees were assessed during study visits at baseline (0 weeks), mid-intervention (6 weeks post-enrollment), and immediately following the intervention (12 weeks post-enrollment) for PROs. Blood collection was achieved by in-person lab visits at the baseline and post intervention time points. The MUSC REDCap system was used for data management. REDCap (Research Electronic Data Capture) is a secure, web-based application designed exclusively to support data capture for research studies [58]. Quality of life was measured using the Lupus Quality of Life measure (LUP-QOL) which incorporates the Medical Outcomes Study (MOS) Short Form 36 Health Survey (SF-36) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). The questionnaire includes questions pertaining to physical function, role function, social function, mental health, health perception and pain [59,60].