Mortality Due to sepsis In Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

Orit Barrett MD[1,2], Ella Abramovich MD[1], Jacob Dreiher MD MPH[4], Victor Novack MD PhD[1,2] and Mahmoud Abu-Shakra MD[1,3]

[1]Department of Medicine D, [2]Clinical Research Center and [3]Rheumatic Diseases Unit, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[4]Clalit Health Services, Beer Sheva, Israel

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Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are chronic systemic autoimmune diseases characterized by articular and a wide range of extra-articular manifestations. Both diseases are remitting-recurring and manifest a broad spectrum of laboratory and clinical features.

SYSTEMIC LUPUS ERYTHEMATOSUS AND INFECTION

The survival rate of patients with SLE has improved significantly over the last five decades, from less than 50% at 5 years in 1955 to 85% at 10 years in recent studies [1]. This improvement in SLE survival rates is the result of a continuously increasing survival in the general population, advances in therapeutic modalities, more judicious use of existing therapies (particularly steroids and cytotoxic agents), and the change in prognostic factors. Despite this encouraging progress, patients with SLE followed at various centers in North America have a 2.4 to threefold increased risk of death compared with the general population. This increased mortality is the result of infections, cardiovascular disease, and irreversible damage to target organs [1].

Infections contribute significantly to the morbidity and mortality of patients with SLE. It is estimated that at least 50% of SLE patients will suffer a severe infectious episode during the course of their disease [2]. Up to 30% of deaths in SLE are due to infections, although a recent mortality study from Hong Kong showed infection to be the main cause of death in 60% of the cases [3]. Similar to infections in the general population, major infections in SLE include common infectious diseases, such as pneumonia, urinary tract infection, cellulites and septicemia. In addition, patients with SLE are susceptible to infections associated with immune suppression, including opportunistic infections, tuberculosis, herpes zoster, as well as disseminated infections. In a study from Sao Paulo, the observed number of deaths due to tuberculosis, septicemia and pneumonia was significantly higher among SLE patients as compared to age- and gender-matched controls [1].

Identifying predictor variables for major infection in SLE is crucial for developing management plans to further improve the survival of SLE patients. A wide range of demographic, clinical and laboratory variables have been associated with increased risk of infections in SLE. These include low socioeconomic status, race, nephritis, antiphospholipid syndrome, high disease activity, damage measures and many others. The degree of immunosuppression and SLE disease are among the most important of those variables [4].

The clinical features of very active SLE may mimic those of infection and occasionally it is difficult to distinguish between SLE infection and SLE flare. Early diagnosis and treatment of a suspected infectious process is highly important since a delay in diagnosis may result in a rapid and fatal course.

RHEUMATOID ARTHRITIS AND INFECTION

RA is a chronic systemic inflammatory disease characterized by proliferative synovitis of diarthrodial joints, serositis, lymphocytic infiltration in various tissues, vasculitis of small vessels, and production of autoantibodies. The management of RA includes the use of non-steroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs, and a variety of biologic therapies. Those therapies are used in combination and this is associated with significant immunosuppression. Indeed, infectious diseases were one of the three leading causes of premature death in several RA cohorts.

Similar to patients with SLE, RA patients are at increased risk for serious infectious disease, including pneumonia, urinary tract infections, septicemia and septic arthritis [5]. Therapy with tumor necrosis factor inhibitors (TNFi) is associated with an increased risk of active tuberculosis (TB). In one study, the gender- and age-adjusted incidence rate of active TB among TNFi-treated patients was 117 per 100,000 patient-years and the standardized incidence ratio (SIR) was 12.2. Tuberculosis developed within a few months of beginning TNFi therapy as a result of reactivation of latent TB infection or due to recent

primary infection following exposure to patients with active TB [6].

Variables associated with significantly increased risk for infection among patients with RA include older age, smoking, and presence of other comorbid diseases such as chronic lung and kidney diseases and diabetic mellitus, as well as the use of immunosuppressive medications [5,7].

SEPSIS

Systemic inflammatory response syndrome (SIRS) is an inflammatory state in which various mechanisms of the immune system are activated. This response is frequently associated with infection. Sepsis refers to the existence of these processes in the presence of infection [8,9]. Sepsis is the second leading cause of mortality among patients admitted to the ICU [9]. During the last decade, there was a steady increase in the incidence rate of sepsis in the general population, and the mortality rate as a result of sepsis is still around 70% [9,10]. Case-fatality rates of patients with sepsis is 1.5 to 2.5-fold more common than those of patients admitted to the ICU due to other causes [9,10]. In 2000, 28 day mortality rates were 7% for SIRS, 16–25% for sepsis and 20–54% for severe sepsis and septic shock. Mortality rates from sepsis correlate with the number of organ systems involved. The mortality rate is 15% risk for death when there is no sign of organ dysfunction or tissue hypoperfusion, and 70% in patients presenting a dysfunction in three or more organ systems [8-10]. Despite the vast number of papers studying infections in SLE and RA, a literature review did not reveal large controlled studies of sepsis in SLE and RA.

Clalit Health Services is the largest health fund in Israel and seven major hospitals are affiliated to this organization. SEPSIS-ISR is an ongoing prospective study that collects data on all patients admitted with the diagnosis of sepsis to the ICUs of all seven Clalit hospitals during the period 2002–2012. From the database we identified all patients with SLE and RA aged 18 years or more who were diagnosed with sepsis and admitted to the general ICU [10].

This ongoing study aims to assess whether SLE and/or RA are independent risk factors for short- and long-term mortality in patients admitted to the ICU with sepsis. Age- and gender-matched subjects with a diagnosis of sepsis but without SLE or RA were selected for each patient with SLE/RA at a 1:3 and 1:2 ratio respectively. The diagnosis of sepsis was based on well-defined criteria.

Correspondence
Dr. M. Abu-Shakra
Dept. of Internal Medicine D, Soroka Medical Center, P.O. Box 151, Beer Sheva, 84101, Israel
Phone: (972-8) 640-0601
Fax: (972-8) 638-3632
email: mahmoud@bgu.ac.il

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