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Interferon alpha (IFN- α) in systemic lupus erythematosus (SLE)

Sara Moqbil, Eryk Mikos, Joanna Dmochowska, Aleksandra Wójcik, Milena Leziak

Medical University of Lublin

Corresponding author: Sara Moqbil, saramoqbil1@gmail.com

Sara Moqbil: <https://orcid.org/0000-0003-1230-1444>, saramoqbil1@gmail.com

Eryk Mikos: <https://orcid.org/0000-0003-0507-2882>, mikoseryk@gmail.com

Joanna Dmochowska, <https://orcid.org/0000-0003-0396-2363>, asia.dmo@gmail.com

Aleksandra Wójcik, <https://orcid.org/0000-0003-1669-7466>, awojcik115@gmail.com

Milena Leziak <https://orcid.org/0000-0001-9911-5534>, milena.leziak@wp.pl

Abstract:

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology. An important role in the pathogenesis of SLE has been attributed to interferon alpha (IFN- α), which stimulates the expression of numerous genes, resulting in an increased autoinflammatory response. Recent studies have demonstrated increased levels of this cytokine in patients with SLE, as well as in relatives, indicating that IFN- α is an inherited risk factor for lupus. Cases of induction of SLE/lupus-like syndrome after IFN- α therapy also point to the involvement of interferon in the pathogenesis of the disease. Interferon being a probable initiator of the disease, as well as a marker to examine its exacerbations, is a potential research target to better understand the etiology and pathogenesis of lupus. More research is needed to determine the feasibility of using INF-blocking agents for new therapies in SLE.

Keywords: systemic lupus erythematosus, interferon alpha, IFN- α -induced SLE

Introduction and purpose

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology, with underlying disorders from the immune system – an abnormal immune system response results in the production of autoantibodies, deposition of immune complexes in tissues, activation of the cytokine system, ultimately leading to tissue destruction and development of organ failure. SLE most often affects women of reproductive age [1]. The disease is a very complex condition due to its multiple clinical and laboratory manifestations. General symptoms of the disease include fatigue, a subfebrile state or fever, and weight loss. SLE also very commonly affects the musculoskeletal system [2]. Dermatological manifestations - malar rash, photosensitivity, discoid rash and alopecia - and symptoms such as lupus nephropathy, neuropsychiatric systemic lupus erythematosus (NPSLE), cardiac and pulmonary serositis, and pericarditis are also common in SLE [3]. The disease runs with periods of exacerbation and remission - various cytokines have been suspected for activating disease regulation. One of the cytokines whose increased presence has been reported in SLE patients is interferon alpha (IFN α). The purpose of this paper is to determine the role IFN- α plays in the etiology and pathogenesis of lupus.

IFN- α in SLE

IFN α is a pleiotropic cytokine (type I interferon) that affects different groups of cells involved in the pathogenesis of lupus. Moreover, the expression of IFN- α -dependent genes increases with disease activity, suggesting a major role for this cytokine pathway in SLE etiology.

Reports of patients whose interferon-alpha therapy induced SLE or lupus-like syndrome have raised the suspect that this cytokine may be responsible for the induction of SLE [4,5]. After 10 months of therapy, a patient with cryoglobulinemic vasculitis associated with hepatitis C virus (HCV) infection developed photosensitive malar rash, arthralgias, lymphopenia, and anti-SSA autoantibodies, which led to the diagnosis - SLE induced by IFN- α therapy [4]. The role of IFN α was also confirmed by the fact that discontinuation of therapy resulted in remission of SLE symptoms.

A fact that supports the hypothesis of the importance of IFN α in the pathogenesis of SLE is the presence of high levels of interferon in the serum of patients with active lupus. Increased levels of interferon were evidenced in 28 patients with SLE (71 percent with active and 21 percent with inactive disease) [6]. IFN levels are significantly correlated with disease manifestation according to the American College of Rheumatology (ACR) criteria. Patients in the IFN-high group had a higher number of SLE criteria (6.8 ± 1.3 compared to 5.7 ± 1.1 in patients with lower interferon levels) [7]. Niewold et al. conducted a study on 266 SLE patients and 405 healthy relatives to compare IFN- α concentrations [8] - healthy family members of SLE patients were reported to also have high IFN- α activity (65 of 359 (18%) first-degree relatives). These findings suggest that high IFN α levels may be a heritable risk factor for SLE.

The role of interferon in SLE can also be observed by the correlation between its levels and the clinical manifestation of the disease. A study of 77 SLE patients revealed that patients with high IFN α levels were far more likely to develop renal disease, as well as have lower levels of C3, hemoglobin, lymphocyte count and albumin levels. A high IFN α score significantly correlated with the presence of lupus-specific antibodies [9].

Elevated IFN scores are also positively associated with lupus nephritis, cutaneous symptoms and the presence of anti-double-stranded DNA (anti-dsDNA) antibodies [10,11].

Conclusions

Numerous reports indicate that IFN α plays a key role in the etiology and pathogenesis of SLE. These reports have prompted a new form of therapies focusing on blocking IFN α . A phase I study of an anti-IFN antibody has demonstrated that this therapy results in inhibition of IFN-dependent gene expression in peripheral blood cells and skin lesions in SLE patients [12]. INF-blocking antibodies are a potentially emerging treatment for SLE, more studies are needed to establish the safety and efficacy of this therapy.

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