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Efficiency of Tocilizumab Therapy for an Exacerbation of Systemic Lupus Erythematosus: A Review of Literature

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Abstract

One of the major proinflammatory cytokines is Interleukin-6 (IL-6), which, during interaction with hepatocytes, provokes the synthesis of a broad spectrum of acute phase inflammatory proteins. IL-6 plays a significant role in the development and progression of systemic lupus erythematosus (SLE), participates in the differentiation of CD4/CD8 regulatory T lymphocytes and in the production of autoantibodies by B lymphocytes, and increases the survival of plasmablasts. Tocilizumab (TCZ) is a humanized anti-IL-6 receptor antibody that neutralizes the pleiotropic effects of the cytokine. The usage of this drug in SLE can be efficient in case high inflammatory activity, accompanied by fever, polyarthritis, polyserositis, skin lesions, and hemolytic anemia. TCZ has a satisfactory safety profile and may be considered as an alternative treatment for SLE when glucocorticoids, cytostatic agents, and rituximab are ineffective.

Keywords: Systemic lupus erythematosus; Tocilizumab; Interleukin-6; Therapy

Introduction

Tocilizumab (TCZ) is a humanized antibody to the interleukin 6 receptor (IL6), which neutralizes the pleiotropic effects of this pro-inflammatory cytokine. Clinical trials and real-world practice have demonstrated high efficacy of TCH in rheumatoid arthritis (RA), Castem's disease and juvenile idiopathic arthritis [1]. It is known that IL6 also plays an important role in the pathogenesis of systemic lupus erythematosus (SLE). Thus, it was shown that a high level of IL6 is associated with the development of glomerulo-nephritis in NZB NZW F1 mice [2,3], and the use of antibodies to IL6 blocks the development of the disease [4,5]. Several papers present encouraging results of THC therapy in patients with SLE with an average degree of activity [6].

IL6 in the Pathogenesis of SLE

IL6, consisting of 184 amino acids, was originally identified as a factor stimulating B-lymphocytes (BSF-2), which promotes the synthesis of immunoglobulins by activated B cells [7]. IL6 plays an important role in the immune system, it is involved in the differentiation of CD4/CD8 T-lymphocytes, T-regulatory cells, of autoantibodies in B lymphocytes, increases the survival of plasmablasts [8]. IL6 is one of the main inflammatory cytokines, which interacting with hepatocytes, induces the synthesis of a wide range of proteins of the acute phase of inflammation: CRP, amyloid (SSA), fibrinogen, hypsidine, α1-antichymotrypsin, and also inhibits the expression of fibronectin, albumin and ferritin [9,10]. According to various data, with SLE observed an increased serum IL6 level [11-13], which correlates with levels of disease activity or anti-DNA. More of that, neutralization of IL6 leads to a significant reduction of the spontaneous synthesis of immunoglobulins [14] and anti- DNA [15]. It is very interesting that in patients with lupus nephritis there is an increased excretion of IL6 in the urine, which decreases after treatment with cyclophosphamide [16,17]. The significant role of IL6 in the development of immune-inflammatory reactions underlying autoimmune diseases predetermined the use in such patients of TCZ-a monoclonal antibody that inhibits transmembrane and soluble IL6 receptors in SLE.

The Use of TCZ in Patients with SLE

In 2010, the first publication devoted to the evaluation of the effectiveness of the TCZ with SLE appeared [18]. In this work preliminary were presented the data of the open clinical study of immunological clinical efficacy of TCZ in 16 patients with SLE. TCZ was used as an infusion every 2 weeks during 12 weeks and continued this therapy up to 20 weeks at doses of 2 mg/kg (4 patients), 4 mg/kg (6) and 8 mg/kg (6). The study included patients with reliable SLE according to the criteria of ACR [18,19], with an average degree of SELENA-SLEDAI activity (4 to 15 points), with a high level of anti-DNA; 7 patients had polyarthritis, 6 had erythema, and 5 had inactive lupus nephritis. The daily dose of prednisolone did not exceed 0.3 mg/kg per day.

Results and Discussion

The following results were obtained at the endpoint of the study, the authors revealed a significant decrease in activity by SLEDAI, the number of swollen joints in the whole group decreased from 7.7 till 5.4 to the 6th week and till 1.1 to the end of the study; In 3 out of 6 patients with skin lesions, erythema was lost at 2-6 weeks of therapy, and 5 patients with kidney damage had an improvement in urinary sediment by the end of the study. Already after the first infusion of TCZ, a significant decrease in the level of acute phase inflammation markers (CRP, ESR, fibrinogen) was observed, statistically significant ($p<0.001$) to the 6th and 14th weeks. No significant changes in the levels of IgM and IgA were detected, while the decrease in IgG at the endpoint of the study was statistically significant. The level of anti-DNA significantly decreased only in the group of patients who received TCZ at a dose of 8 mg/kg. Interesting data were obtained by the authors when analyzing the effect of TCZ therapy on immunocompetent cells: the level of lymphocytes, as well as T and B lymphocytes in peripheral blood, did not change during the whole observation, while the number of CD38 +++ IgD-plasma cells was significantly lower at the end of the study

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compared to the baseline [18,20]. In general, TCZ therapy was well tolerated. Among the side effects in patients of all groups, there was a dose-dependent neutropenia, not accompanied by the development of infections, the number of neutrophils independently restored till the end of the study. Infections of the upper respiratory tract and urinary tract occurred in 11 patients during 14 weeks of observation, if necessary; they were stopped by the use of antibiotics and antiviral drugs and in no case did not interfere with TCZ therapy.

It is known that therapy with inhibitors of tumor necrosis factor alfa (TNF α) in patients with SLE can cause an increase in the level of anti-DNA, ANF [20-22]. Moreover, Soforo E et al. [21] reported the development of SLE in 6 patients with RA and psoriatic arthritis treated with TNFα inhibitors. The authors suggest that therapy with TNFα inhibitors can lead to cell necrosis with the release of nuclear components, the formation of antinuclear antibodies, and the development of SLE. In connection with this, it is of interest to observe Adler S et al. [23] who described the development of SLE in a patient with granulomatous polyangiitis after 7 Infliximab infusions. The use of pulse therapy with 6-methylprednisolone and RTM in this patient was effective, but not long enough, reducing the dose of prednisolone led to recurrence of scleritis and a significant increase in the level of CRP and ESR. In this case, the infusion of TCZ led not only to the rapid arrest of clinical manifestations (symmetrical polyarthritis, scleritis, pericarditis, endocarditis, and myositis), normalization of the level of anti-DNA, complex, CRP and ESR, but also to the development of remission for a long time, 1 year.

Maeshima K et al. [24] reported the successful use of TCZ in the patient with RA and SLE (Overlap-syndrome). The authors describe a 37-year-old woman with seropositive (RF +, ACPC +) RA in combination with prednisolone and MT -therapy who developed clinical and laboratory signs of SLE (pericarditis, nephritis, high-positivity ANF, anti-DNA and anti-Sm, hypocomplementemia, thrombocytopenia). RA activity according to DAS28 was 7.6 points. Due to the high activity of the disease, the patient received pulse therapy, prednisolone 50 mg/day, infusions of cyclophosphamide with an insufficient and short-term effect. In connection with relapses of polyarthritis, thrombocytopenia and high immunological activity, tacrolimus 2 mg/day and TCZ 400 mg/month were added to the therapy. Combined therapy led to a rapid and persistent decrease in the activity of the disease: normalization of the level of anti-DNA, reduction in the level of ANP, normalization of platelet count in peripheral blood, persistent polyarthritis arrest (decrease of DAS28 from 7.6 to 1.8 points) and decrease daily dose of prednisone to a minimum. The observation during 6 months did not reveal the development of side effects against the daily dose of tacrolimus in a dose of 2 mg and monthly infusions of TCZ by 400 mg.

A great interest reveals the data of Iwai A et al. [25] on the effectiveness of TCZ in multi-organ failure. The authors observed a patient with SLE and Sjogren's syndrome with the development of glomerulonephritis, pericarditis, arthritis, erysipes, thrombocytopenia, with high immunological activity (high level of anti-DNA, decrease in the concentration of C3 and C4 components of complement, polyclonal Hypergammaglobulinemia) and inadequate efficacy of combination therapy with high doses of prednisolone (50-80 mg/day), etanercept (50 mg/week) and tacrolimus (3 mg/day), which was manifested by persistent high fever, massive effusion in pericardium and increasing proteinuria. Laboratory studies revealed leukopenia, high serum ferritin and CRP, and a high IL6 content in pericardial swelling and serum. After the prescription of TCZ in a dose of 8 mg/kg every 2 weeks, rapid disappearance of pericarditis, complete normalization of the level of CRP and ferrimuth, normalization of the content of anti-DNA and an increase in the level of complement were observed. The therapy of TCZ was continued, and cyclophosphamide was added to stop the nephritis. In total, the patient received 5 infusions of TCZ and 3 infusions of cyclophosphamide. Over the next 6 months the patient's condition remained consistently satisfactory, the normal level of immunological indices and markers of inflammation remained. There was no exacerbation of the disease; the dose of prednisolone was reduced to 5 mg/day.

The positive results of THC therapy in the development of pericarditis in patients with SLE are of great practical importance due to the insufficient effectiveness of even high doses of HA [26]. Minota Y and Kamata S [27] describe a patient with SLE with recurrent pericarditis, ineffectiveness of high doses of prednisolone and tacrolimus, repeated drainage of the pericardial cavity with introduction of betamethasone into the pericardial cavity. Before the beginning of TCZ therapy, the level of IL6 in the pericardial fluid was 1160 pg/ml, in the serum-6.1 pg/ml at a rate <4 pg/ml. TCZ was prescribed at a dose of 400 mg/month. Already after 1 month, a significant decrease in the fluid in the pericardium and an improvement in laboratory activity, including a decrease of anti-DNA level, were noted. The TCZ therapy was continued up to 2.5 years, the drug was injected 1 time every 5 weeks for 19 months, then - once every 6, 7 and 8 weeks. During the time of observation there were no recurrences of pericarditis or other manifestations of SLE activity; the dose of prednisolone was reduced from 15 to 5 mg/day.

Another manifestation of SLE that is no less difficult for therapy is a recurrent lesion of the skin [28]. Makol AT et al. [29] demonstrated the effectiveness of TCZ therapy in a patient with SLE with a common erythematous skin lesion and urticarial vasculitis with ineffectiveness of high doses of prednisolone and mycophenolate mofetil (MMF). In this observation, only 2 infusions of TCZ with an interval of 1 month contributed to the almost complete disappearance of skin lesions, normalization of body temperature, a decrease in laboratory activity indices and decrease a prednisolone dose of up to 5 mg/day.

Of practical interest are the data of F. Garcia-Hernandez et al. [30] who reported the efficacy of TCZ in a patient with SLE and hemolytic anemia recurring despite the use of massive doses of HA and RTM. The appointment of the TCZ at a dose of 8 mg/kg per month in combination with MMF led to a normalization of the hemoglobin and reticulocyte levels within 1 month after the initiation of therapy. Continuation of THC therapy at a dose of 4 to 8 mg/kg per month contributed to the development of persistent remission and a decrease in the dose of HA to a minimum.

Conclusion

Thus, TCZ has an acceptable efficacy in SLE with high inflammatory activity, accompanied by fever, polyarthritis, polyserositis, skin damage and hemolytic anemia. The use of the TCZ in a standard dose of 8 mg/kg per month contributes to rapid relief of extrarenal manifestations of SLE, normalization of the level of CRP, and a decrease in the daily dose of prednisolone. The phenomenon of a decrease of immunological activity of SLE, the normalization of the level of anti-DNA and the increase in the content of complement fractions in SLE require further study, in particular a possible mechanism for blocking the function of antibodies-producing cells. In this respect, the specific biological function of IL6 (stimulation of the final phase of maturation of B-lymphocytes in plasma cells and, as a consequence an increase in production of immunoglobulins and autoantibodies) is of interest

[31]. Several studies have revealed a correlation between an increase of IL6 level, SLE activity, and an increase of anti-DNA concentration [32,33]. In addition to systemic effects, IL6 can act locally, as evidenced by its presence in the cerebrospinal fluid in patients with CNS lesions (neyrolubus) [34]. TCZ has a satisfactory safety profile and can be considered as an alternative method of therapy for SLE in the case of insufficient effect of CS, cytostatics and RTM. The role and place of the TCZ in recommendations for SLE therapy should be clarified in subsequent open and controlled clinical trials.

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