CLINICAL OBSERVATIONS

Use of rituximab in the of immunoinflammatory rheumatic diseases combined with Graves' disease (autoimmune polyglandular syndrome in adults): case report and literature review

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Rituximab (RTM) is a chimeric (murine and human) monoclonal antibody against B-lymphocytes (CD20). RTM is widely used in hematology for lymphoproliferative diseases and in rheumatology for rheumatoid arthritis, Sjögren's disease, some types of vasculitis and systemic connective tissue diseases. The administration of RTM is associated with a depletion of B-cells mediated by the regulation of apoptosis and cytotoxic effects via complement-dependent and antibody-dependent mechanisms. Considering the pathogenesis of autoimmune damage in Graves' disease (GD), an autoimmune thyroid disease associated with thyrotoxicosis, the use of RTM could be effective in this pathology.

We present three patients with a combination of diffuse toxic goiter and rheumatic pathology treated with RTM; different outcomes of GD were observed.

Keywords: *rituximab; Graves' disease; diffuse toxic goiter; systemic lupus erythematosus; systemic scleroderma; microscopic polyangiitis.*

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Graves' disease (GD), or diffuse toxic goiter, is an autoimmune disease that develops as a result of the production of antibodies to the thyroid-stimulating hormone receptor (anti-TSH), clinically manifested by damage to the thyroid gland (TG) with the development of thyrotoxicosis syndrome in combination with extrathyroid pathology (Graves' orbitopathy – GO – pretibial myxedema, arthropathy) [1]. The main symptoms of GD include emotional lability, tachycardia, hand tremor, weight loss, etc. The absence of adequate treatment can lead to persistent heart rhythm disturbances with the development of atrial fibrillation, as well as thyrotoxic liver damage. Treatment of GD involves the administration of antithyroid drugs in order to achieve stable euthyroidism for at least 2 years, followed by a trial withdrawal to assess the stability of remission. In this case, immunosuppressive therapy for suppression of the autoimmune process in GD in the absence of GO is not prescribed.

Rituximab (RTM) is a chimeric (mouse and human) monoclonal antibody to B-lymphocytes (CD20) and is widely used in hematology for the treatment of lymphoproliferative diseases. In rheumatology, RTM is used to treat rheumatoid arthritis, Sjogren's disease, some types of vasculitis and systemic connective tissue diseases [2]. The introduction of RTM is accompanied by B-cell depletion due to the regulation of apoptosis and the cytotoxic effect mediated by complement-dependent and antibody-dependent mechanisms [3]. Considering the pathogenesis of autoimmune damage in GD, an autoimmune disease of the thyroid gland, accompanied by thyrotoxicosis, the use of RTM can be effective in this pathology [4].

In 2003, due to the possible involvement of B-lymphocytes in the pathogenesis of GO, the use of RTM for the treatment of the active phase of moderate to severe course of the disease was first proposed [5].

A frequent combination of autoimmune thyroid damage with other autoimmune diseases was noted, and vice versa, thyroid pathology is often encountered in immune-inflammatory rheumatic diseases. Taking this into account, the term "autoimmune polyglandular syndrome of adults type 3" or "multiple autoimmune syndrome" was proposed [6, 7]. It is important to emphasize that RTM is not registered for the treatment of GD and is prescribed exclusively outside clinical indications (off-label).

This publication presents a description of 3 patients with diffuse toxic goiter without GO, who underwent RTM therapy for a rheumatic disease with varying effects on GD. All of them gave their consent for the publication of anonymized information from their case histories. In the Russian Federation, RTM is registered for the treatment of the following rheumatic diseases: rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis. In 2 of the 3 presented cases, RTM therapy for systemic lupus erythematosus (SLE) and systemic scleroderma in combination with Sjogren's syndrome was used after a consultation and a medical expert commission on the administration of genetically engineered biological drugs.

Clinical case 1

Patient A.*, a 28-year-old woman, diagnosed with microscopic polyangiitis 6 years ago, received rituximab therapy at 1000 mg twice a year for about 5 years with stable remission. Simultaneously with the detection of rheumatic disease, diffuse toxic goiter was detected with a maximum thyroid volume of up to 43 ml (the norm for women is up to 18 ml) and a level of antibodies to the TSH receptor of up to*

17 U/l (the norm is 0–1 U/l). After the diagnosis was established, therapy with thiamazole 30 mg/day was prescribed with a gradual dose reduction to 5 mg/day and subsequent complete discontinuation after 1.5 years; stable remission was noted. Two years after the cessation of thiamazole treatment, the scheduled RTM therapy was not performed. Against this background, a relapse of thyrotoxicosis was registered, which was manifested by a decrease in TSH to 0.001 IU/l (0.4–4.0 IU/l). Therapy with thiamazole was resumed, and a planned administration of rituximab 1000 mg was carried out as part of the treatment of microscopic polyangiitis. During a dynamic examination after 3 months, normalization of the TSH level, as well as free T3 and T4, was observed, and thiamazole therapy was completely discontinued. During a dynamic examination after 6 months, stable remission of GD was maintained.

Clinical case 2

***Patient K.**, 31 years old, came to the Federal State Budgetary Scientific Institution "V.A. Nasonova Research Institute of Rheumatology" (V.A. Nasonova Research Institute of Rheumatology) with complaints of hair loss, the appearance of a "butterfly" exanthema on the skin of the face, weight loss, tachycardia. About 3 years ago, she was diagnosed with SLE and prescribed therapy with prednisolone up to 30 mg/day, which the patient subsequently stopped taking on her own. A year and a half ago, she was diagnosed with GD, and therapy with thiamazole was initiated and then discontinued after 1 year, which led to a relapse of thyrotoxicosis. Thiamazole intake was resumed, after which an adverse drug reaction (exanthema) developed, and the drug was replaced with propylthiouracil up to 100 mg/day without a significant effect. Due to subsequent detection of leukopenia (white blood cell count 1.6 $\cdot 10^9$/l), the drug was discontinued. Upon repeated examination by a rheumatologist, the diagnosis of chronic SLE, moderate activity, with manifestations in the form of diffuse alopecia, Jaccoud syndrome, skin lesions, mucous membranes, kidneys and hematological disorders was confirmed. Due to high activity of SLE, the patient was hospitalized to V.A. Nasonova Research Institute of Rheumatology, where therapy with RTM 1000 mg 2 times with an interval of 2 weeks and prednisolone 20 mg/day was prescribed. After normalization of the white blood cell count, propylthiouracil 200 mg/day was resumed, thyrotoxicosis was relieved. According to the ultrasound data, the thyroid volume was 44.8 ml, the anti-rTSH level was 31.0 IU/l. After 3 months, against the background of normalization of the TSH, free T3 and T4 levels, an attempt was made to reduce the dose of propylthiouracil to 100 mg/day, which was accompanied by a relapse of thyrotoxicosis and a decrease in the TSH level to 0.008 IU/l.*

Clinical case 3

***Patient D.**, 40 years old, diagnosed with systemic scleroderma, limited form, chronic course, with interstitial lung disease and Sjogren's syndrome, established 5 years ago, with previously diagnosed GD, for which she took thiamazole for 6 years, consulted an endocrinologist at V.A. Nasonova Research Institute of Rheumatology. About 2 years ago, therapy with RTM 1000 mg once every 6 months was started for the treatment of systemic scleroderma. Laboratory examination revealed euthyroidism, thyroid volume – 14.8 ml, anti-rTSH – 1.1 U/l, and due to the low risk of relapse it was recommended to discontinue thiamazole. According to the control analyses in dynamics after 3 and 6 months, the euthyroid status was maintained (normal levels of TSH, as well as free T3 and T4 were detected).*

Discussion.

RTM was first used for diffuse toxic goiter in 2006 [8]. In 2007, the results of the first study of 20 patients receiving antithyroid drugs (n=10) or a combination of antithyroid therapy and RTM for GD were published. After 1 year of observation, 4 out of 10 patients in the combination therapy group achieved stable euthyroid status, while in the monotherapy group – only 1 out of 10 patients [9].

In another study, which included 13 patients who were observed for 27 months, RTM therapy at a dose of 1000 mg administered twice with an interval of 2 weeks was accompanied by the achievement of euthyroid status of GD in 69.2% of patients [10].

As shown by the results of another prospective study of 27 patients with GD aged 12–20 years, after a single administration of RTM at a dose of 500 mg and subsequent use of antithyroid drugs, a high rate of remission (48.1%) was also noted after 2 years of observation, with an average general population level of achieving euthyroidism of 20–30% [11].

The anti-rTSH titer can be used as one of the prognostic factors for achieving stable remission of GD, and has a positive correlation with the severity of GO [12]. One of the studies revealed a significant decrease in the anti-rTSH titer after the administration of RTM in patients with GD, which, however, did not lead to a change in the activity or severity of GO [13]. In another study, therapy of GD with antithyroid drugs in combination with RTM contributed to a longer maintenance of remission compared to monotherapy with antithyroid drugs, and clinical improvement was not accompanied by a significant decrease in the level of anti-rTSH. Moreover, in both groups, the decrease in the anti-rTSH titer was comparable (on average by 15%) [14]. However, not all studies recorded such an effect [15, 16]. In a meta-analysis of 12 studies in a total of 152 patients with GO who received RTM therapy, a limited effect of the drug on GO was found, but a significant decrease in the anti-rTSH titer was noted after 6 and 12 months of observation [17]. Taking into account the presented conflicting data on the effect of RTM on the titer of thyroid-stimulating antibodies, it can be assumed that their level cannot be used to assess the effectiveness of treatment.

This publication describes 3 women with various rheumatic diseases and concomitant GD who were prescribed RTM; however, the course of GD during therapy with this drug was fundamentally different. In clinical observation № 1, the positive effect of RTM on GD is most likely, given the initially high risk of ineffectiveness of conservative therapy due to a significant increase in the thyroid gland and a high titer of antibodies, as well as the development of a relapse when the next infusion of this drug is missed. In clinical observation № 2, the use of RTM did not allow achieving remission of GD. In clinical observation № 3, it is difficult to assess the direct effect of RTM on the disease itself, since at the time of the last examination, the patient already had a normal thyroid gland volume and low titers of anti-rTSH, and the course of diffuse toxic goiter in some cases can be accompanied by achieving remission 2 years after the start of treatment with thyreostatics.

Conclusion. The presented data certainly cannot serve as a basis for independent prescription of RTM to patients with GD in the absence of other diseases requiring its use. Further study of the course of GD in a larger cohort of patients with an immune-inflammatory rheumatic disease requiring the prescription of RTM may be promising.

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Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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