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Autoimmune disorders and thyroid function in patients with rheumatoid arthritis after biological treatment

ABSTRACT

Rheumatoid arthritis (RA) and autoimmune diseases of the thyroid gland (AITD) often occur together. As autoimmune diseases, they share common pathological pathways, reflecting the fact that the treatment of the underlying disease can influence the course of thyroid disorders. The pharmacotherapy of RA is based on the supply of disease-modifying anti-inflammatory drugs with an increasing focus on biologics. This article aims to review the available literature describing the effects of biological treatments on thyroid function. The use of biological

drugs may have the potential benefit of regulating the level of anti-thyroid antibodies. On the other hand, tumour necrosis factor-alpha (TNF- α) inhibitors are not indifferent to thyroid function and may increase the incidence of subacute thyroiditis. The coexistence of AITD and RA prompts consideration of the need for routine thyroid screening in RA patients and for RA screening in patients with thyroid disease who report joint problems.

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KEY WORDS: autoimmune thyroid disease; rheumatoid arthritis; biological treatment; TNF-alpha inhibitors; Grave's ophthalmopathy

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes joint damage and deterioration in the quality of life [1]. As an autoimmune disease, it tends to coexist with other autoimmune diseases, with autoimmune thyroid disease (AITD) being the most common [2]. Rheumatoid arthritis and AITD also have a common autoimmune pathomechanism mediated by self-reactive T lymphocytes and other immune cells. In addition, studies indicate combined genetic predispositions such as human leukocyte antigen (HLA) haplotypes and cytotoxic T cell antigen 4 (CTLA4) gene polymorphisms [3]. There have been reports of the occurrence of specific antithyroid antibodies in RA, which also suggests an interaction between the two diseases [4].

Rheumatoid arthritis is a progressive and incurable disease with a multi-stage treatment. The aim is to achieve remission, but an untargeted approach to treatment leads to the side and systemic effects associated with the use of glucocorticoids. Therefore, biological drugs are of great importance although their effect on other organs is still under investigation [5].

Multiple pathomechanisms are common in RA and thyroid diseases, and therefore drugs targeting a particular pathway in RA may also affect thyroid function. An example is the tumour necrosis factor-alpha (TNF- α) inhibitors. There have been reports of induction of subacute thyroiditis with the use of these drugs, especially during the COVID-19 (coronavirus disease 2019) pandemic [6], as well as normalization of anti-thyroid antibody levels following treatment with these drugs [7].

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This report focuses on the biological drugs used in RA and their effects on thyroid function. In addition, it discusses the use of RA treatment-approved medicines in the treatment of thyroid diseases.

AITD: TWO WAYS OF THYROID AUTOIMMUNITY

Autoimmune thyroid diseases occur in approximately 5% of the population, and they are associated with a higher risk of other autoimmune disorders [8]. There are two main autoimmune thyroid diseases. Hashimoto's thyroiditis (HT), also called chronic lymphocytic or autoimmune thyroiditis and Graves' disease (GD). The incidence of hypothyroidism is estimated at 350/100 000/year in women and 80/100 000/year in men, while hyperthyroidism occurs in 80/100 000/year in women and 8/100 000/year in men [9]. However, these data should be approached with caution as the causes of thyroid disease were often not specifically identified.

Since HT can present in various forms such as focal lymphocytic infiltration with only antithyroid antibodies present and atrophic thyroiditis leading to its failure, a proper diagnosis might be challenging [10]. The clinical presentation of HT may also influence the determination of its frequency.

Both diseases will develop with the coexistence of genetic predisposition, the interaction of environmental factors, and the loss of immunological tolerance to one's tissues. The exact mechanisms underlying hereditary tendencies are not fully understood. It is assumed that AITDs are caused by the interaction of several genes and their inheritance is complex [10].

Much research has set out to discuss this issue. Tomer and Davies [10] prospected for susceptibility genes to autoimmune thyroid diseases and found that some of them may be immune-modifying genes that generally increase vulnerability to autoimmunity (e.g. HLA and CTLA4). In contrast, others may be AITD specific (e.g. TSHR — the thyroid-stimulating hormone receptor, thyroglobulin, CD40- cluster of differentiation 40) [10].

Environmental factors have been identified as risk factors for thyroid autoimmunity. They cause injuries that contribute to activating the innate immune response resulting in the appearance of autoantigens — the main ones in thyroid disease are thyroid peroxidase (TPO), thyroglobulin (TG), and thyroid-stimulating hormone receptor (TSHR). Un-

der normal conditions, own thyroid antigens will not elicit an inflammatory response, but there is an abnormal immune response in people with impaired T lymphocyte function. The cytotoxic CD8+ and B cells are stimulated by activated CD4+ T lymphocytes, transforming into plasma cells and forming antithyroid antibodies against various antigens. In the last stage of HT, the autoreactive T-cells infiltrating the thyroid gland mediate the destruction of the gland by cytotoxicity, and macrophages produce cytokines which, together with antibodies, initiate the destruction of thyroid cells by apoptosis [11].

Generally, in Hashimoto's thyroiditis, pathology is mainly caused by T cells, while GD is determined by B lymphocytic response [11].

As the HT progresses, the clinical picture changes. Rarely, in the initial phase, mild or moderate hyperthyroidism can be observed. This phenomenon is referred to as "Hashitoxicosis". The reason is an excess hormone output from the thyroid cells damaged by the lymphocytes, but ultimately this results in the development of hypothyroidism [12]. The main symptoms of hypothyroidism include fatigue, bradycardia, weight gain, constipation, brittle nails, hair loss, joint pain, stiffness, muscle weakness, cold intolerance, and depression. The primary goal of HT treatment is to restore euthyroidism by supplementing levothyroxine [12]. In the course of GD, a combination of thyrotoxicosis, goitre and ophthalmopathy is observed. The classic triad does not occur in all patients, and often the only noticeable symptom is hyperthyroidism [13]. Patients with GB may experience agitation, heat intolerance, tremors, and weight loss. In the elderly, subtle symptoms are common, such as fatigue, mood disturbances, or shortness of breath (referred to as "apathetic thyrotoxicosis") although sometimes much more serious symptoms can occur, including atrial fibrillation, congestive heart failure, or acute ischaemic heart syndrome [14]. Patients should be initially treated with antithyroid drugs, and if radical therapy is needed, radioiodine or thyroidectomy should be considered [13].

RHEUMATOID ARTHRITIS

The most common chronic autoimmune joint disease is RA, with an estimated incidence of 51/10000 [15]. Rheumatoid arthritis is first characterized by joint involvement followed by extra-articular symptoms such as

rheumatoid nodules, keratoconjunctivitis, pulmonary and pleural involvement, pericarditis and atherosclerosis [16].

The RA pathomechanism has not yet been fully elucidated. Both genetic and environmental factors are considered [17]. It is expected that an innate tendency toward autoimmune reactions combined with a triggering event such as infection or tissue damage results in the activation of previously formed auto-reactive lymphocytes [17]. The most important genetic risk factors include *HLA-DB1* genes encoding class II tissue compatibility antigens [18]. Polymorphisms in the genes of cytokines and signalling molecules of lymphocytes may also contribute to RA susceptibility or increase the severity of the disease [5]. Non-gene risk factors are also numerous. They include components that affect the respiratory tract, such as cigarette smoke, viral and bacterial infections, asthma, and exposure to occupational inhalation of silica. In addition, obesity increases the risk of developing RA. An expanding role in the pathogenesis of RA is attributed to the microbiome. Periodontal diseases, in particular those caused by *Porphyromonas gingivalis*, are more common in people with RA [19].

Predisposing factors contribute to the dysregulation of citrulline by modifying autoantigens (converting arginine residues of proteins to citrulline) and generating antibodies to citrullinated proteins (ACPA), which are believed to be the underlying theory of the

RA mechanism. The immune system is unable to correctly recognize citrullinated proteins due to the involvement of HLA-predisposing genes. APCs begin to present peptides from autoantigens to T cells, which then activate macrophages and fibroblasts in the affected joint. Inflammation develops through the secretion of large amounts of pro-inflammatory cytokines. Autoreactive T lymphocytes also activate B lymphocytes to produce ACPA and autoantibodies to the rheumatoid factor. These autoantibodies further potentiate inflammation by directly activating macrophages or triggering the complement cascade. These processes lead to synovitis of the joints and bone erosion [17].

Anti-citrullinated proteins antibodies are highly specific to RA, while rheumatoid factor can be observed in healthy elderly people and patients with other autoimmune diseases or infections. Antibodies to carbamylated protein (anti-CarP) and anti-acetylated protein antibodies are also detected. The presence of antibodies can be detected many years before the inflammatory response is evident as clinical joint symptoms. This attribute may be useful in detecting future RA patients [20].

THYROID ANTIBODIES AND RA

In addition to the specific antibodies mentioned above, patients with RA have a higher risk of antithyroid antibodies and autoimmune thyroid diseases [21].

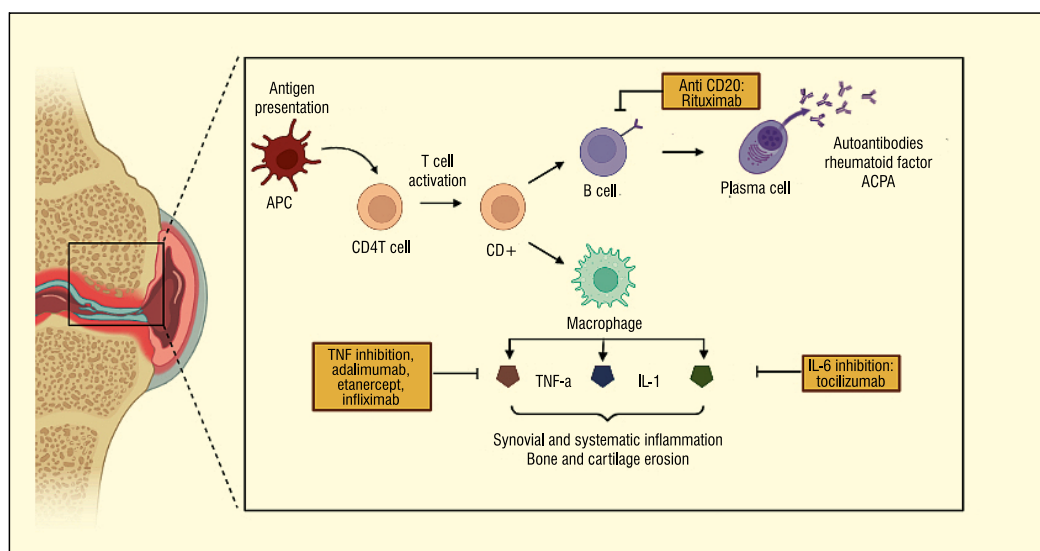


Figure 1. A simplified diagram of the cytokines and receptors which are the targets for biological drugs in RA that affect thyroid function. Pro-inflammatory cytokines release (TNF- α , IL-1, IL-6) and ACPA are critical for the initiation of RA pathogenesis. They cause chronic inflammation and consequent damage to the articular cartilage and bone erosion. ACPA — anti-citrullinated protein antibody; APC — antigen-presenting cells; CD20 — cluster of differentiation 20; IL-1 — interleukin-1; IL-6 — interleukin-6; RA — rheumatoid arthritis; TNF- α — tumour necrosis factor-alpha

Pan et al. [4] attempted to determine the prevalence of antithyroid antibodies in RA patients. A study involving 1021 patients with RA and 1500 healthy patients revealed that the presence of thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) in patients with RA were higher than in healthy controls, with odds ratios of 3.1 and 2.3, respectively. These observations suggest that thyroid autoimmunity is more common in RA patients than in the general population. The prevalence of antithyroid autoantibodies in patients with RA varies between studies. TgAb's prevalence ranged from 5% in men from the United Kingdom [22] to 31% in RA patients from Japan [23]. On the other hand, TRAb has been rarely reported in immune diseases other than the thyroid gland. Koszarny et al. [24] did not detect them in any of the 75 RA patients. Moreover, other authors suggest that the thyrotropin receptor antibodies (TRAbs) are specific only to GD and some patients with Hashimoto's thyroiditis [25]. However, Nakamura et al. [23] confirmed the presence of TRAb in 2 of the 29 RA patients, corresponding to 6.9%. Likewise, the incidence of immunoglobulin G antibodies to triiodothyronine and thyroxine was compared in the 3 autoimmune diseases: HT, GD, and RA, reaching 20, 30, and 26%, respectively [26].

THE CO-OCCURRENCE OF AITD AND RA

Several studies have confirmed that the co-existence of AITD and RA in the same patient is not uncommon [27–30]. It seems that autoimmune diseases tend to concentrate due to a defect in maintaining immune tolerance [21].

According to Boelaert et al. [27], the frequency of another autoimmune disorder with AITD is 9.67% in GD and 14.3% in HT index cases, and among them, the most common co-occurring autoimmune disorder was RA (found in 3.15% of GD and 4.24% of HT cases).

In the study by Ferrari et al. [28] containing 3209 GD patients, 1.9% suffered from RA. In Hungary, the incidence was reported in 4.9% of patients [29] and in China as high as 32.3% [30]. The relationship between thyroid dysfunction and RA has not always been consistently documented in the literature, although data from the American trial showed no significant difference in hypothyroid and hyperthyroid disease incidence in the cohort study pooling 650 RA patients and a similar number of healthy adults [31]. Data from Po-

land [32] reported that AITD was more common (16%) in RA patients than in the control group (9%) and their clinical symptoms were less severe. The dominant thyroid dysfunction was subclinical hypothyroidism (7% vs. 5% respectively in the study and control group), and both subclinical and symptomatic hyperthyroidism did not exceed 2%.

Due to the frequent coexistence of AITD and RA, the mutual influence was sought. Chen et al. [33] demonstrated that joint damage can be enhanced in RA patients with elevated thyroid autoantibodies. Attention was focused on indicators, such as tender joint count based on a 28-joint assessment (TJC28) and disease activity, including Disease Activity Score 28-joint erythrocyte sedimentation rate (DAS28-ESR) and the Clinical Disease Activity Index (CDAI). All these indicators were significantly higher among RA patients in the TAbs (thyroid autoantibodies)-positive group compared with patients in the TAbs negative group. Similar to the study by Koszarny et al. [24], a relationship has been established between TPOAb, DAS28 and TgAb, and also between both C-reactive protein and ESR. Furthermore, DAS28 was significantly higher in the TPOAb/TGAb-positive group. In summary, the results presented point to an association between antithyroid antibody titres and RA activity and point to the need for monitoring thyroid function in patients with RA.

TNF- α AS AN INDICATOR OF THE CONDITION OF THE THYROID GLAND

Cytokines are a heterogeneous group of proteins showing high biological activity which transmit information between cells. They can affect the growth and differentiation of follicular cells of the thyroid gland leading to thyroid dysfunction [34, 35]. TNF- α is a cytokine mainly regulated by the inflammatory response and its production is stimulated, among others, by nicotinamide phosphoribosyltransferase/visfatin [36]. Therefore, excessive or improper TNF- α production may cause certain inflammations and autoimmune diseases [35]. The relevance of activation of the TNF- α system in patients with thyroid diseases was confirmed with an increase of TNF- α in both hyperthyroidism and hypothyroidism compared to the control group [34, 37]. Besides, treatment of hyperthyroidism was accompanied by normalization of TNF- α levels, in contrast to hypothyroidism, where no differences in

TNF- α values were found [34]. However, other studies showed no significant difference in serum TNF- α levels between GD patients and healthy controls [35] or lower TNF- α levels in GD patients [38]. Considering TNF- α is a secretory product of fat tissue, it is plausible to think that weight loss due to hyperthyroidism caused these results [38].

As already mentioned, TNF- α is involved in the pathogenesis of autoimmune diseases. Therefore, inhibiting its activity with antibodies has become an essential treatment method. As the biological treatment (TNF- α inhibitor) has been used more and more, an increased prevalence of subacute thyroiditis (SAT) has been documented [39]. The pandemic of coronavirus disease 19 has shown that the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can also be a potent SAT-triggering factor [6]. However, no association of coronaviruses with SAT development has been reported before the pandemic [40].

The significant finding in the study of Nakagawa et al. [39] was that SAT could be developed during only TNF- α inhibitor treatment. There were no previous reports of SAT associated with other biologic disease-modifying anti-inflammatory drugs (DMARDs) or targeted synthetic DMARDs, such as an IL-6 receptor inhibitor (tocilizumab), cytotoxic T cell antigen 4- Ig (abatacept), IL-17 inhibitors, IL-23 inhibitors or the Janus kinase inhibitors. The exact mechanism by which TNF- α inhibitors induce SAT is not fully understood. It is assumed that increased production of TNF- α by plasmacytoid dendritic cells as a result of biological treatment promotes lymphocyte migration and inflammatory reaction [41]. Another explanation may be related to cytokine imbalance triggered by TNF- α inhibitors [39].

TREATMENT OPTIONS FOR RA AND POSSIBLE EFFECTS ON THYROID FUNCTION

Rapid therapy initiation may prevent irreversible disabilities in up to 90% of patients with RA. Treatment aims to achieve remission or a state of low disease activity. Primary pharmacological agents are disease-modifying anti-inflammatory drugs (DMARDs), which are divided into conventional synthetic (csDMARDs), targeted synthetic (tsDMARDs), and biological (bDMARDs) [42].

According to the recommendations of the European League Against Rheumatism

(EULAR) [43] and the American College of Rheumatology 2021 [44], methotrexate (MTX) is the first-line drug. In case of contraindications to MTX, sulfasalazine or leflunomide is recommended. When initiating therapy, the administration of glucocorticosteroids is indicated to relieve symptoms before the development of the activity of DMARDs. Glucocorticoids should be used in the lowest effective dose and the shortest possible time to avoid side effects. The next stage of treatment in patients who have not achieved optimal results is the addition of bDMARD or tsDMARD. Targeted synthetic DMARDs work by inhibiting the activity of one or more enzymes belonging to the Janus kinase (JAK) family. Examples of drugs include tofacitinib, baricitinib, filgotinib, and upadacitinib. On the other hand, bDMARDs include abatacept, rituximab, tocilizumab, sarilumab, and TNF- α such as infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol [45]. If the therapy still does not bring the desired results, bDMARD/tsDMARD should be changed to another, or in the case of prior treatment with TNF- α , a switch to a drug with a different mode of action or another TNF- α may be considered [43].

BIOLOGICAL DMARDS AND THYROID FUNCTION

Many factors influence the success of RA treatment. A Swedish cohort study showed that AITD was associated only with a subjectively worsened measure of disease activity. A group of patients with concomitant AITD treated with primary MTX were compared to patients without this comorbid disease. AITD does not appear to affect the likelihood of a good response to treatment. The only exception was the group of young patients in whom AITD seemed to reduce MTX response [46].

However, it appears that biological treatment of RA as an autoimmune disease may influence the course of the underlying disease and other autoimmune comorbidities. In a systematic review, Bliddal et al. [7] analysed data on the treatment of patients with TNF- α or rituximab. A non-significant trend towards a slight improvement in both thyroid function and autoantibody status was observed. A tendency to decrease TPOAb and TgAb levels and to decrease TSH levels in patients with hypothyroidism has been shown.

There are no consistent reports of the effects of TNF- α inhibitors on thyroid function.

Both positive effects of therapy on AITD and negative effects have been reported [47].

ADALIMUMAB

Atzeni et al. [48] analysed a group of 20 patients, including 6 anti-TPO-positive and 8 anti-TG-positive patients. After 6 months of follow-up, anti-TPO antibodies were negative in only one patient. Results suggest that the incidence of organ antibodies remained unchanged after treatment with adalimumab. Raterman et al. [49] also investigated thyroid function at the beginning of treatment with adalimumab and after 6 months. Decreased anti-TPO and TSH levels have been observed in patients with RA and untreated hypothyroidism

INFLIXIMAB

The study by Elkayam et al. [50] aimed to analyse different types of autoantibodies in RA after treatment with infliximab. The anti-TPO concentration was negative in the entire group of 26 patients. After 14 weeks of treatment, anti-TPO levels were re-examined and no change in antibody titres was observed. Kaklamanos et al. [51] examined the specific effects of rituximab and infliximab on the thyroid gland. Similarly, no significant changes in thyroid function or antibody titre changes were observed. Only an increased index of thyroid vascularization was shown in ultrasound as well as decreased echogenicity, which may suggest the progression of AITD. Slightly different results were reported by Caramaschi et al. [52]. A group of 43 patients was evaluated for thyroid antibodies at the start of the study and after 12 months of treatment with infliximab. In 4 cases, the titre changed from positive to negative and in 6 cases from negative to positive without any patients developing clinical signs of autoimmune thyroiditis. In addition, 6 patients had a positive anti-TG titre and 7 patients had a positive anti-TPO titre throughout the study. All but one patient were treated with infliximab.

ETANERCEPT

Caramaschi et al. [52] also evaluated patients treated with etanercept. Of the 13 patients, only 1 had a positive anti-thyroid antibody titre at baseline. No antibody titre change was observed in any of the patients during the study. Apart from this study, there

are few reports of the effects of etanercept on the thyroid gland in the treatment of RA. The literature describes the case of a 50-year-old woman who developed subacute thyroiditis while using bDMARDs [53]. The patient presented a daily fever of unknown origin and neck tenderness around the thyroid gland. Etanercept was discontinued and treatment with oral prednisolone was started, resulting in symptom relief. Another case was reported by Andrés et al. [54]. A 43-year-old woman treated with TNF- α developed silent thyroiditis. Decreased TSH levels, and positive antithyroid titres without clinical symptoms were observed. Etanercept treatment was discontinued 4 months after the onset of hypothyroidism as well as after one and a half year of follow-up without hormone replacement and without worsening of the disease.

BIOLOGICAL TREATMENT IN THYROID GLAND DISORDERS

In describing the effect of biological drugs used in RA on the thyroid gland, it is worth mentioning their growing role in the treatment of thyroid diseases. An example is their use as second-line therapy in Graves' ophthalmopathy (GO). GO is classified into 3 degrees of severity: mild GO, moderate-to-severe GO and sight-threatening GO [55]. Mild GO has a slight impact on daily life. Usually, one or more of the clinical symptoms such as minor lid retraction (< 2 mm), exophthalmos < 3 mm above normal for race and gender, intermittent or no diplopia and corneal exposure responsive to lubricants are present. Moderate-to-severe GO is reasonable to initiate immunosuppressive therapy if the disease is active. Patients usually present two or more of the symptoms such as inconstant or constant diplopia, lid retraction ≥ 2 mm, moderate or severe soft-tissue involvement, and exophthalmos ≥ 3 mm above normal for race and gender. The most severe degree of GO requires immediate treatment and is manifested by optic neuropathy and/or corneal damage [55, 56].

The aim of the treatment in moderate to severe and active GO is to mute the active phase and relieve ocular symptoms. With the ineffectiveness of the first-line treatment in the form of glucocorticosteroids and sodium mycophenolate or mycophenolate mofetil, biological treatment was started [55, 57].

Table 1. Summary of the reviewed publications — effects of biological treatment of rheumatoid arthritis on thyroid function

	References	n	Conclusion of the study
Adalimumab	Atzeni et al. [48]	20	The incidence of organ antibodies does not appear to change with adalimumab treatment. After 6 months of follow-up, only one of the 6 positive patients had a negative anti-TPO titre
	Raterman et al. [49]	38	After 6 month of treatment, decreased anti-TPO and thyroid-stimulating hormone levels have been observed in patients with rheumatoid arthritis and untreated hypothyroidism
Infliximab	Caramaschi et al. [52]	43	Heterogeneous changes in antithyroidism antibodies have been observed. In 4 patients, the titre changed from positive to negative, in 6 patients from negative to positive, without developing clinical symptoms
	Kaklamanos et al. [51]	18	No significant changes in antithyroid antibody titre in entire group of patients were observed
	Elkayam et al. [50]	26	The anti-TPO concentration was negative in the entire group of 26 patients. After 14 weeks of treatment, anti-TPO levels were re-examined and no change in antibody titres was observed
Etanercept	Caramaschi et al. [52]	11	No antibody titre change was observed in any of the patients during the study

n — number of patients

RITUXIMAB

Rituximab (RTX) is a chimeric, humanized monoclonal antibody against CD20, an antigen found on B lymphocytes in both mature and immature B cells. By acting specifically on B cells, RTX may affect autoantibodies directed against TSH receptors, the elevated level of which was observed at the beginning of the active phase of GO [58].

Stan et al. [59] in a prospective randomized trial attempted to determine the efficacy of RTX in GO. Twenty-one patients assigned to the two groups received either two 1000 mg RTX infusions or 2 saline infusions at two-week intervals. There were no significant differences between the clinical activity score (CAS) in the RTX and placebo-treated groups after 24 and 52 weeks of follow-up. Another randomized study by Salvi et al. [60] compared the effectiveness of RTX and methylprednisolone. Thirty two patients were randomized to receive RTX (2000 mg or 500 mg) or intravenous methylprednisolone (7.5 g). After 16, 20 and 24 weeks, improvement in clinical activity was seen in both groups, but more pronounced in the RTX group. No relapse was observed in the RTX group, whereas recurrence appeared in 5 patients treated with glucocorticoid. Deltour et al. [61] also observed the effectiveness of RTX in the treatment of GO. RTX seems to be effective, especially in patients with recently diagnosed active disease.

Additionally, the meta-analysis of Chen et al. [62], Shen et al. [63], and Wang et al. [64] confirmed the promising effects of RTX treat-

ment in Grave's orbitopathy. RTX improves both CAS and the level of anti-thyroid antibodies but shows no significant changes in the improvement of exophthalmia. Studies have highlighted the heterogeneous occurrence of side effects which requires further studies depending on the dose of the drug.

TOCILIZUMAB

Tocilizumab is a humanized recombinant monoclonal antibody directed against the interleukin-6 receptor. Interleukin-6 (IL-6) is secreted by many cells, including T lymphocytes, macrophages, and fibroblasts. One of its actions is the activation of B cells and the development of plasma cells that produce antibodies. In addition, it also acts directly on the preadipocytes of the eye socket and promotes volume enlargement [55, 65].

Pérez-Moreiras et al. [66] evaluated the effectiveness of tocilizumab in 18 patients who had failed glucocorticoid therapy. Fifteen patients had improved extraocular mobility and in 7 out of 13 patients, the diplopia had subsided. However, the results were limited by a small study group and a non-randomized study design. In the following years, a double-blinded randomized clinical trial was conducted [67]. Thirty two patients with GO resistant to glucocorticoids were randomized to the placebo group or to receive intravenous tocilizumab at a dose of 8 mg/kg body weight. Significantly more patients (93.3%) achieved a CAS change of at least 2 points in the tocilizumab group than in the control group (58.8%). A reduction

in proptosis was also observed in the treatment group, which was not the case in the control group. The results suggest that tocilizumab provides an effective clinical improvement in glucocorticoid-resistant moderate to severe and active GO. Similar conclusions were also reached by Sánchez-Bilbao et al. [68]. Low disease activity was achieved in 92.6% of cases and tocilizumab treatment was discontinued in 29 cases of which 25 were due to low disease activity and 4 were due to lack of response. Also, no serious side effects were observed. A recent study found statistically significant reductions in the CAS, Thyroid-Related Ophthalmopathy Score and Thyroid Stimulating Immunoglobulin levels when comparing pre-treatment values. None of the patients relapsed to active disease after stopping tocilizumab treatment [69].

TNF- α inhibitors also have been used in the treatment of GO. Research suggests the utility of TNF- α inhibitors in suppressing the clinical symptoms of GO and reducing CASs such as adalimumab, etanercept, and infliximab. However, there are no randomized clinical trials available on the use of these drugs in GO. Larger group studies are needed to determine the efficacy of TNF- α inhibitors as an alternative treatment for GO compared to glucocorticosteroids [70, 71].

CONCLUSIONS

This review aims to illustrate the relationship between the biologics used and their effects on the thyroid gland. Due to the frequent coexistence of AITD and RA, in patients reporting joint complaints despite restoration of euthyroidism, RA should be considered. Additionally, screening for thyroid gland dysfunction in patients with RA is worth considering. Biologic RA therapy may have a potentially positive effect on AITD by reducing anti-TPO antibody titres, but there are no studies to confirm its clinical significance. TNF- α inhibitors used in RA patients increase the risk of subacute thyroiditis.

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CONTRIBUTIONS

Conceptualization — NSG; DW, NZ and NSG wrote the manuscript; AE and MR corrected the manuscript and approved the final version of the manuscript. All authors have read and approved the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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