

Anti-tumour necrosis factor α therapy – Does it increase the risk of thyroid disease or protect against its development?

Terapia z zastosowaniem przeciwciał przeciwko czynnikowi martwicy nowotworów α – zwiększa ryzyko chorób tarczycy czy chroni przed ich rozwojem?

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Abstract

Aim of the study: Tumour necrosis factor α (TNF- α) is a cytokine involved in the pathogenesis of many diseases, primarily those associated with autoimmunisation. Anti-TNF- α drugs are used in the therapy of many of them, such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, or inflammatory bowel disease. TNF- α is also a key factor in the pathogenesis of autoimmune thyroid disease (AITD). The incidence of AITD in people with other autoimmune diseases is increased compared to the general population. Therefore, it would be interesting to find out if anti-TNF- α therapy of other autoimmune diseases could influence the possible development or regression of thyroid gland dysfunction, especially AITD.

Aim of the study: The main aim of the study is to assess the effect of anti-TNF- α therapy used in inflammatory and immunological diseases on thyroid function and the development of AITD.

Conclusions: The real impact of anti-TNF- α therapy on the development of AITD remains an open question. The available studies concern the adult population; there are no data regarding this problem in children. Due to the increasing use of anti-TNF- α therapy also in the paediatric population, it seems reasonable to evaluate this subject in this group of patients.

Key words:

TNF- α , anti-TNF- α therapy, autoimmunisation, AITD.

Streszczenie

Wprowadzenie: Czynnik martwicy nowotworów α (*tumor necrosis factor α* – TNF- α) to cytokina biorąca udział w patogenezie wielu chorób, przede wszystkim tych, które rozwijają się na podłożu autoimmunizacji. W terapii wielu z nich, takich jak reumatoidalne zapalenie stawów, łuszczycowe zapalenie stawów, zeszywniające zapalenie stawów kręgosłupa, łuszczyca czy nieswoiste choroby zapalne jelit, stosowane są leki określane mianem anty-TNF- α . Czynnik martwicy nowotworów α jest także kluczowym czynnikiem biorącym udział w patogenezie autoimmunizacyjnej choroby tarczycy.

Częstość występowania autoimmunizacyjnej choroby tarczycy u osób chorujących na wyżej wymienione choroby jest zwiększona w porównaniu z populacją ogólną. Stwarza to pytanie o wpływ terapii anty-TNF- α na ewentualny rozwój zaburzeń czynności i morfologii gruczołu tarczowego, w tym szczególnie autoimmunizacyjnej choroby tarczycy.

Cel pracy: Głównym celem pracy jest ocena wpływu terapii anty-TNF- α , stosowanej w chorobach zapalnych i immunologicznych, na czynność tarczycy i rozwój autoimmunizacyjnej choroby tarczycy.

Wnioski: Pytanie o wpływ terapii anty-TNF- α na rozwój autoimmunizacyjnej choroby tarczycy wciąż pozostaje bez konkretnej odpowiedzi. Ponadto dostępne badania dotyczą populacji osób dorosłych. Z uwagi na coraz szersze zastosowanie terapii anty-TNF- α także w populacji pediatrycznej, zasadne wydaje się objęcie badaniami także tej grupy pacjentów.

Słowa kluczowe:

TNF- α , terapia anty-TNF- α , autoimmunizacja, AITD.

Introduction

Tumour necrosis factor α is an important cytokine of inflammatory and immunological reactions, it is involved in the pathogenesis of many diseases, including autoimmune diseases [1, 2]. This fact has become the basis for the search for new therapeutic options for patients suffering from diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, or inflammatory bowel diseases. Hence, anti-TNF- α drugs were created, the main task of which is to reduce the concentration of TNF- α and thereby inhibit the cascade of phenomena occurring in the course of its action, which can lead to the development of the disease. TNF- α is also a key factor involved in the pathogenesis of thyroid disease, including AITD.

As is known from the available literature, the incidence of AITD in people with other autoimmune diseases, such as rheumatoid arthritis or inflammatory bowel disease, is increased compared to the general population. Therefore, it would be interesting to know if anti-TNF- α therapy of other autoimmune diseases could have an influence on possible development or regression of thyroid gland dysfunction, especially AITD.

Aim of the study

The main aim of the study is to assess the effect of anti-TNF- α therapy used in inflammatory and autoimmunological diseases on thyroid function and the development of AITD.

Discussion

TNF- α , described for the first time by Carswell *et al.* in 1975, also known as cachectin, is an important cytokine of inflammatory and immunological reactions [1, 2]. The TNF- α gene, located on chromosome 6p21.3, consists of four exons, and its promoter region shows very high variability, which determines the differentiated cytokine secretion in individuals [1]. Active TNF- α consists of three polypeptide chains, and it is formed as a result of a metalloproteinase (TNF- α -converting enzyme) action on its precursor synthesised as a transmembrane protein. TNF- α is mainly produced by monocytes and macrophages. Its source can also be lymphocytes, mast cells, fibroblasts, keratinocytes, endothelial cells, cardiomyocytes, or thyroid cells [1, 3–5].

The main stimulators of TNF- α production are lipopolysaccharides (LPS) of bacterial cell wall. In addition, TNF- α synthesis is stimulated by other cytokines such as INF- α and IL-1. Also, TNF- α in an autocrine manner stimulates its own synthesis. Glucocorticosteroids, IL-4, IL-10, and PGE2 are inhibitors of TNF- α production [1,6].

TNF- α has affinity for two types of receptors: TNF-R1 (CD120a, p55 / 60) and TNF-R2 (CD120b, p75/80). They both, in their intracellular part, contain a so-called death domain. TNF-R1 is activated by both free and transmembrane forms of TNF- α . TNF-R2 binds mainly to transmembrane forms of TNF- α . TNF- α receptors also differ in their location: TNF-R1 is located

on nuclear cells, and TNF-R2 on immune cells, fibroblasts, and endothelial cells. In addition, expression of TNF- α receptors is increased by interleukin 1 (IL-1), interferon γ (INF- γ), IL-2, and TNF- α alone [1]. After binding of TNF- α to the TNF-R1 receptor, the protein inhibitor SODD (silencer of death domain) is disconnected from the intracellular death domain, which allows activation of the TRADD protein (TNF-R-associated death domain) and further signal transduction steps. These stages can be carried out in three ways, depending on the connection of TRADD with subsequent relays. As a result of the attachment to the TNFR1-TRADD of the FADD (Fas-associated death domain) adapter protein, the caspase cascade (mainly 8, 3, 7) is activated, which ultimately leads to cell apoptosis [7]. As a result of the attachment to TNFR1-TRADD of RIP (receptor-interacting protein) and/or TRAF2 (TNF receptor-associated factor 2) transmitters, a cascade of kinases is activated, including the κ B inhibitor kinase (I κ B), which is released by phosphorylation of I κ B NF- κ B cytoplasm, and its further activities at the level of the cell nucleus primarily lead to cell activation and prevent apoptosis [7]. The third way is through attachment to the TNFR1-TRADD of the TRAF2 adapter protein and the activation of the MEKK1 (Mitogen activated protein kinase/ERK kinase 1) system, which induces the so-called JNK trail (c-Jun N-terminal kinase). The JNK pathway usually leads, through the transcription factor AP-1, to cell stimulation and proliferation. However, there is also evidence of a proapoptotic effect of JNK pathway activation [8].

TNF- α is an extremely powerful mediator of inflammatory and immunological reactions. It can act independently or in combination with a wide range of other cytokines, affecting almost all cells in the body. TNF- α increases the cytotoxicity and phagocytic properties of cells of the immune system, it affects the proliferation and differentiation of B lymphocytes, T lymphocytes, and NK cells, and increases the synthesis of cytokines. In addition, it induces the expression of MHC I, MHC II, and adhesive particles and chemokines necessary for the accumulation of immune cells at the site of inflammation [1].

The indisputable influence of TNF- α on the immune system makes it a key factor in the pathogenesis of many diseases, including autoimmune diseases. This fact has become the basis for seeking new therapeutic options for patients suffering from diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, or inflammatory bowel diseases. As a consequence of the knowledge of this phenomenon, anti-TNF- α drugs were created, the main task of which is to directly reduce the concentration of TNF- α and thereby inhibit the cascade of phenomena occurring in the course of its action.

TNF- α inhibitors are monoclonal antibodies, antibody fragments, or fusion proteins. This group of biological drugs includes the following: infliximab (IFX), which is a monoclonal, chimeric, human-mouse (75%: 25% protein structure) IgG1-class antibody with a molecular weight of 149 kDa; adalimumab (ADA), which is a purely human class antibody; IgG1 with a molecular weight of 148 kDa; certolizumab (CER), which is a humanised Fab fragment (approximately 90% human) of polyethylene glycol conjugated monoclonal antibody (PEG); and etanercept (ETA), which is a fusion protein composed of

the extracellular portion of the TNFR2/p75 receptor (this portion binds TNF- α) fused to the IgG1 Fc fragment [9].

TNF- α is also involved in the pathogenesis of thyroid dysfunction, including AITD. As many authors report, the concentration of TNF- α and TNF- α mRNA in the thyroid tissue in people with AITD and other thyroid gland disorders is definitely higher compared to people without those disorders. Thyroid infiltrating lymphocytes are a reliable source of TNF- α ; moreover, TNF- α production by thyroid cells alone has been reported. Zheng *et al.* [5] proved that thyroid cells are capable of producing TNF- α ; Grubeck-Loebenstein *et al.* [10] did not show the presence of TNF- α mRNA in thyroid cells; and Diez *et al.* [4] showed an increased concentration of TNF- α in the thyroid tissue of people with AITD, but they did not specify its source (lymphocytes or thyrocytes). Thyroid cells have receptors for TNF- α on their surface, and it is postulated that TNF- α plays an essential role in cytotoxic mechanisms leading to the destruction of thyroid tissue in AITD [4]. This cytokine is responsible for the increase in the expression of MHC class I molecules on thyroid cells in Graves' disease and, together with INF- γ , for the increase in MHC class II expression [11, 12]. TNF- α has been shown to increase IL-6 production by thyroid cells [13]. TNF- α affects the tightness of thyrocyte epithelium, which leads to a loss of its barrier function and an increase in the access of immune cells to intravesical antigens [14, 15]. In addition, TNF- α inhibits the production of thyroglobulin [16], reduces TSH-induced iodine uptake by thyroid cells [17], reduces type 2 deiodinase activity, which leads to a decrease in peripheral production of triiodothyronine from thyroxine, and also reduces autocrine production of triiodothyronine in the thyroid alone [18, 19]. TNF- α also influences the function of the hypothalamus-pituitary-thyroid axis. TNF- α inhibits TRH, which reduces the secretion of TSH [20]. The mechanisms described above are also involved in the pathogenesis of low T3 syndrome (euthyroid sick syndrome), which may accompany severe chronic diseases for which an increase in TNF- α is typical [20].

Due to the fact that diseases in which anti-TNF- α therapy is used are associated with a higher risk of developing AITD compared to the general population [21, 22] and that TNF- α plays a role in the aetiopathogenesis of thyroid dysfunction, one would expect that anti-TNF- α therapy would have a protective effect against the possible development of AITD, and would be therapeutic if it is present.

There are few reports in the available literature about the development of thyroid dysfunction during anti-TNF- α therapy. In addition, it provides very diverse data (Table I). Cerniglia *et al.* reported the development of hypothyroidism in a 47-year-old patient treated with infliximab for sarcoidosis. The ultrasound image of the thyroid gland corresponded to autoimmune thyroid disease. The authors postulated that the cause of AITD in the patient was the formation of autoantibodies (against infliximab) that induced autoimmune thyroiditis [23]. Lahita *et al.* described a 55-year-old patient who developed autoimmune thyroiditis during long-term anti-TNF- α therapy for psoriatic arthritis. Based on elevated TSH levels before starting anti-TNF- α

therapy, the authors suggested that autoimmune thyroiditis may have occurred before treatment. Nonetheless, anti-TNF- α therapy led to the progression of autoimmune thyroiditis [24]. Van Lieshout *et al.* are the authors of a report on the development of Graves' disease in a patient treated with anti-TNF- α for rheumatoid arthritis [25]. Similarly, Allanore *et al.* reported a transient hyperthyroidism lasting one month in a patient after six months of treatment with etanercept [26]. Caramaschi *et al.* described a group of 54 patients with rheumatoid arthritis, among whom six changed the titre of anti-thyroid peroxidase antibodies (ATPO) or anti-thyroglobulin antibodies (aTG) from negative to positive, and four from positive to negative, after 12 months of therapy with infliximab or etanercept [27]. Atzeni *et al.*, in a study of 20 patients (including six with positive ATPO and eight with positive aTG) with rheumatoid arthritis, showed a change in ATPO from positive to negative in one of the patients after six months of treatment with adalimumab [28]. Pascart *et al.* examining patients treated with anti-TNF- α due to rheumatological diseases in their centre, described 11 cases of development of AITD, including six cases of Graves' disease, three cases of Hashimoto's disease, and two cases of subacute thyroiditis [29]. Raterman *et al.*, in a group of 138 patients with rheumatoid arthritis, after six months of treatment with adalimumab, described a change in the ATPO titre from positive to negative in one of 21 patients with a positive ATPO at baseline. They also indicated a lower average ATPO concentration after therapy (267 to 201 IU/ml). In addition, two patients with hypothyroidism reported a return to euthyroidism. They also showed a decrease in TSH (from 12.5 mU/l [6.7–18.4] to 7.1 mU/l [4.9–13.8]) in patients with hypothyroidism, who were ATPO positive and not receiving levothyroxine [30]. Elkayam *et al.*, in a study group of 26 patients with rheumatoid arthritis, described a negative ATPO titre in all patients before and after 14 weeks of treatment with infliximab [31]. Tarhan *et al.*, in a study of 108 patients with ankylosing arthritis spine (44 received anti-TNF- α , 64 received other drugs), reported a positive ATPO titre in 23 patients not treated with anti-TNF- α (mean ATPO 86.69 ± 65.28 U/ml), compared to nine patients receiving anti-TNF- α (mean TPO 36.61 ± 14.02 U/ml) [32]. Paschou *et al.* studied a group of 41 patients (18 treated with anti-TNF- α , 12 treated with other drugs followed by anti-TNF- α , 11 treated only with other drugs) with Crohn's disease or ulcerative enteritis. They found overt or subclinical hyperthyroidism in two patients in the untreated anti-TNF- α group and no thyroid dysfunction or AITD in patients receiving anti-TNF- α . In addition, they showed the presence of thyroid antibodies in 5.6% of patients treated with anti-TNF- α and in 17.4% of those treated with other drugs [33].

Analysing the impact of anti-TNF- α therapy on thyroid function and the development of autoimmune thyroid disease, it is also worth paying attention to the role of TNF- α and anti-TNF- α therapy in thyroid-associated ophthalmopathy (TAO). According to the data, TNF- α is involved in the pathogenesis of TAO [34]. For this reason, anti-TNF- α therapy is increasingly being used to treat TAO. Paridaens *et al.*, in their pilot study, presented 10 patients with mild to moderate Graves' ophthalmopathy treated with etanercept for 12 weeks. In this study, 60% of patients had moderate to marked improvement of TAO after this

Table I. Effect of anti-TNF- α therapy on thyroid function – summary of available publications

The negative effect of anti-TNF- α therapy used in inflammatory and immunological diseases on thyroid function and the development of AITD	The positive effect of anti-TNF- α therapy used in inflammatory and immunological diseases on thyroid function and the development of AITD	The neutral effect of anti-TNF- α therapy used in inflammatory and immunological diseases on thyroid function and the development of AITD
Cerniglia <i>et al.</i> 2013 [23] development of hypothyroidism in a 47-year-old patient treated with anti-TNF- α therapy for sarcoidosis	Caramaschi <i>et al.</i> 2006 [27] changed the titre of ATPO or aTG from positive to negative, after 12 months of therapy with anti TNF- α for rheumatoid arthritis in four patients from group of 54 patients	Elkayam <i>et al.</i> 2005 [31] negative ATPO titre in all 26 patients before and after 14 weeks of treatment with anti-TNF- α for rheumatoid arthritis
Lahita <i>et al.</i> 2011 [24] progression of autoimmune thyroiditis in a 55-year-old patient during long-term anti-TNF- α therapy for psoriatic arthritis	Raterman <i>et al.</i> 2011 [30] change in the ATPO titre from positive to negative in one of 21 patients in a group of 138 patients with rheumatoid arthritis after 6 months of treatment with anti TNF- α lower average ATPO concentration after therapy (267 to 201 IU/ml) two patients with hypothyroidism reported a return to euthyroidism decrease in TSH (from 12.5 mU/l (6.7–18.4) to 7.1 mU/l [4.9–13.8]) in patients with hypothyreosis, ATPO positive, and not receiving levothyroxine	
Van Lieshout <i>et al.</i> 2008 [25] development of Graves' disease in a patient treated with anti TNF- α for rheumatoid arthritis	Tarhan <i>et al.</i> 2013 [32] positive ATPO titre in 9 patients receiving anti-TNF- α (mean ATPO 36.61 \pm 14.02 U/ml) compared to 23 patients not treated with anti TNF- α (mean ATPO 86.69 \pm 65.28 U/ml) due to ankylosing arthritis spine (44 received anti-TNF- α , 64 other drugs)	
Allanore <i>et al.</i> 2001 [26] development of transient hyperthyroidism in a patient treated with anti-TNF- α for rheumatoid arthritis	Paschou <i>et al.</i> 2018 [33] no thyroid dysfunction or AITD in patients receiving anti-TNF- α compared to development overt or subclinical hyperthyroidism in two patients in the untreated anti-TNF- α group of 41 patients (18 treated with anti TNF- α ; 12 treated with other drugs followed by anti TNF- α ; 11 treated only with other drugs) with Crohn's disease or ulcerative enteritis presence of thyroid antibodies in 5.6% of patients treated with anti-TNF- α and in 17.4% treated with other drugs.	
Caramaschi <i>et al.</i> 2006 [27] changed the titre of ATPO or aTG from negative to positive, after 12 months of therapy with anti-TNF- α for rheumatoid arthritis in 6 patients from a group of 54 patients		

Table I. Effect of anti-TNF- α therapy on thyroid function – summary of available publications (cont.)

<p>The negative effect of anti-TNF-α therapy used in inflammatory and immunological diseases on thyroid function and the development of AITD</p>	<p>The positive effect of anti-TNF-α therapy used in inflammatory and immunological diseases on thyroid function and the development of AITD</p>	<p>The neutral effect of anti-TNF-α therapy used in inflammatory and immunological diseases on thyroid function and the development of AITD</p>
<p>Pascart <i>et al.</i> 2014 [29] development of thyroid diseases in 11 patients (six cases of Graves' disease, three cases of Hashimoto's disease and two cases of subacute thyroiditis) treated with anti-TNF-α due to rheumatological diseases</p>		

anti-TNF- α – anti-tumour necrosis factor α ; AITD – autoimmune thyroid disease; ATPO – anti-thyroid peroxidase antibodies; aTG – anti-thyroglobulin antibodies; TSH – thyroid-stimulating hormone

treatment [35]. Boskovic *et al.* presented a female patient with both Graves' ophthalmopathy and rheumatoid arthritis, who was treated with etanercept. This treatment led to an improvement of eye symptoms [36]. Komorowski *et al.* found a positive effect of Infliximab administration on active TAO in a 58-year-old woman with Graves' disease [37]. These findings suggest that anti-TNF- α therapy may benefit patients with TAO, but all of the mentioned authors point out the necessity of larger studies to confirm its efficacy and safety [38].

Conclusions

Research on biological anti-TNF- α drugs dates back to the 1990s. According to the cited data, despite the relatively long observation time, the question about the impact of anti-TNF- α

therapy on the development or regression of AITD remains open. In addition, according to our knowledge, all available studies concern the adult population. Due to the increasing use of anti-TNF- α therapy also in the paediatric population, it seems reasonable to evaluate this group of patients regarding this subject.

In our clinical centre, anti-TNF- α treatment of children and adolescents with inflammatory bowel diseases is carried out. We are currently in the process of investigating the effect of anti-TNF- α therapy on thyroid gland function and morphology in children and adolescents with Crohn's disease treated with infliximab. The first preliminary results are promising. They indicate that anti-TNF- α treatment may reduce the incidence of AITD in paediatric patients with Crohn's disease compared to non-biological patients.

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