Clinical Update in Aspects of the Management of Autoimmune Thyroid Diseases

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Aspects of autoimmune thyroid disease updated in this review include: immunoglobulin G4 (IgG4)-related thyroid disease (Riedel’s thyroiditis, fibrosing variant of Hashimoto’s thyroiditis, IgG4-related Hashimoto’s thyroiditis, and Graves’ disease with elevated IgG4 levels); recent epidemiological studies from China and Denmark indicating that excess iodine increases the incidence of Hashimoto’s thyroiditis and hypothyroidism; immunomodulatory agents (ipilimumab, pembrolizumab, nivolumab) activate immune response by inhibiting T-cell surface receptors which down-regulate immune response, i.e., cytotoxic T-lymphocyte antigen 4 and programmed cell death protein 1 pathways; alemtuzumab is a humanised monoclonal antibody to CD52 which causes immune depletion and thyroid autoimmune disease especially Graves’ hyperthyroidism; small molecule ligand (SML) agonists which activate receptors, SML neutral antagonists, which inhibit receptor activation by agonists, and SML inverse agonists which inhibit receptor activation by agonists and inhibit constitutive agonist independent signaling have been identified. SML antagonism of thyroid-stimulating hormone-receptor stimulatory antibody could treat Graves’ hyperthyroidism and Graves’ ophthalmopathy; and thyroxine treatment of subclinical hypothyroidism can produce iatrogenic subclinical hyperthyroidism with the risk of atrial fibrillation and osteoporosis. The increased risk of harm from subclinical hyperthyroidism may be stronger than the potential benefit from treatment of subclinical hypothyroidism.

Keywords: Immunoglobulin G; Iodine; Immunomodulation; Hashimoto disease; Thyroxine

INTRODUCTION

This is a brief update of selected clinical aspects of autoimmune thyroid disease (AITD). These aspects are:

1. Immunoglobulin G4 (IgG4)-related thyroid disease (IgG4-RTD)
2. Drug-induced AITD
3. Papillary thyroid carcinoma (PTC) and Hashimoto’s thyroiditis (HT)
4. Selenium therapy
5. Small molecule ligand (SML) thyroid-stimulating hormone (TSH)-receptor antagonist therapy
6. Aspects of therapy in hypothyroid HT

IMMUNOGLOBULIN G4 RELATED THYROID DISEASES

IgG4 related diseases (IgG4-RD) are a new disease category,
which can involve many organ systems including the endocrine system, and the thyroid in particular. IgG4-RD are characterized by frequent elevation of serum IgG4, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, tumefactive lesions with storiform fibrosis, and a rapid response to glucocorticoids [1]. The initial identification of IgG4-RD was in 2001, when sclerosing pancreatitis was associated with high serum IgG4 levels, and response to glucocorticoid therapy [2]. IgG4-RD unifies diseases such as Mikulicz’s syndrome, retroperitoneal fibrosis, Kütter’s tumor, and Riedel’s thyroiditis (RT) [3]. Serum IgG4 levels are usually elevated to greater than 135 mg/dL in IgG4-RD, but this elevation is neither necessary nor adequate for diagnosis. Nevertheless, measurement of serum IgG4 is useful to assess treatment response and recurrence [4].

The pathogenesis of IgG4-RD remains poorly understood but involves genetic factors [5], antigen-antibody reactions, and allergic phenomena [6]. Whether IgG4 plays a central role in pathogenesis of IgG4-RD or is the result of the fibroinflammatory process remains unclear, because IgG4 antibodies are unable to form immune complexes and activate the complement system.

IgG4-RTD was first identified as hypothyroidism with positive thyroglobulin (Tg) antibody in autoimmune pancreatitis patients [7]. Four types of IgG4-RTD have so far been identified: RT, fibrosing variant of Hashimoto’s thyroiditis (FVHT), IgG4-related Hashimoto’s thyroiditis (IgG4-RHT), and Graves’ disease with elevated IgG4 levels (IgG4-GD) [8].

Imaging in IgG4-RTD may support the diagnosis, but findings are not specific for the disease. Ultrasound of the thyroid usually shows diffuse low echogenicity of the thyroid gland in IgG4-RHT, whereas non-IgG4 thyroiditis is associated with diffuse coarse echogenicity [9].

RT was linked with other fibrosclerotic diseases and thought to be a part of IgG4-RD, due to the extensive thyroidal fibrosis and the discovery of associated organ involvement such as retroperitoneal fibrosis [10], pancreatic fibrosis, mediastinal fibrosis, orbital pseudotumour [11], and sclerosing cholangitis [12]. Elevated serum IgG4 levels have not been documented in RT.

The FVHT, is seen in about 10% of patients with HT [13]. Distinctive clinical features of FVHT include a very firm thyroid gland, severe pressure symptoms in the neck, and rapid thyroid enlargement. Compared to typical HT, there is more hypothyroidism, a higher mean IgG4 positive cell count in affected thyroid tissue, and a higher ratio of IgG4/IgG [14].

IgG4-RHT as an entity was proposed in 2009 by Li et al. [15], as a IgG4-positive plasma cell-rich group, in comparison to a non-IgG4 thyroiditis which is a IgG4-positive plasma cell-poor group. Unlike RT, it has not been associated with other systemic manifestations of IgG4-RD. IgG4-RHT is associated with more rapid progress, subclinical hypothyroidism (SCH), diffuse low echogenicity on ultrasonography, and a higher level of circulating thyroid autoantibodies than non-IgG4 thyroiditis [16]. The incidence is unknown.

IgG4-GD is a small subset of patients with Graves’ disease and elevated serum IgG4 levels. These patients are older and have more hypoechoic areas on ultrasonography, but histological differences have not so far been systematically evaluated [17].

**DRUG-INDUCED THYROID DISEASE**

Over the years a variety of therapeutic agents have induced thyroid disease. This can be by by iodine contamination, e.g., cloquinol, contrast agents, amiodarone; by immune modulation, e.g., interferon (IFN), and new agents in this group are the ipilimumab, pembrolizumab, nivolumab, and alemtuzumab.

**Iodine**

Iodine is an essential trace element required for thyroid function and synthesis of thyroid hormone. The recommended adult daily iodine intake is 150 μg, increasing to 220 μg in pregnancy and 270 μg in lactation. Excess iodine has been shown to increase the incidence of HT and hypothyroidism. Recent epidemiological studies from China and Denmark have confirmed this association.

The cumulative incidence of supranormal serum TSH levels in subjects with high levels of anti-thyroid peroxidase (TPO) or anti-Tg increased with increasing iodine intake across three areas in China with environmentally mild iodine deficiency, adequate iodine, and excess iodine [18]. In the longitudinal population-based DanThyr study [19] subjects were examined at baseline (1997 to 1998) and re-examined 11 years later (2008 to 2010) after initiation of a mandatory program for iodization of salt in 2000. Mean TSH increased significantly and the most pronounced increase was observed in the area with the highest iodine intake. Change in TSH was positively associated with the presence of TPO antibody at baseline. Even small differences in the level of iodine intake were associated with considerable differences in TSH change in follow-up.

Iodine supplementation is believed to increase the prevalence of circulating anti-TPO. The underlying mechanism is yet to be elucidated; however, more highly iodinated Tg is more antigenic in experimental autoimmune thyroiditis [20].

Hypothyroidism induced by iodine in AITD may be due to a persistent inhibitory effect of iodine on thyroid hormone synthe-
sis and secretion, i.e., a pathologically persistent Wolff-Chaikoff effect [21]. High iodine supplementation in HT should be discouraged as it is of no benefit and may possibly cause harm. Discouraging iodine mega-supplementation may not preclude appropriate physiological supplementation in pregnancy to a total intake of 250 μg/day.

**Interferon**

IFN-α-induced thyroiditis may be immune-mediated (the presence of antithyroid antibodies has a 67% positive predictive value for the development of thyroiditis) or non-immune-mediated: direct hepatitis C virus effect on thyrocytes. IFN-α immune-mediated thyroid disease is associated with the generation of antithyroid antibodies (in 10% to 40%), which tend to persist after IFN therapy. The induction of HT tends to remit after IFN therapy but the induction of Graves’ hyperthyroidism tends to persist after IFN therapy [22]. IFN-α promotes major histocompatibility complex (MHC) class I expression on thyrocytes and MHC class I expression activates cytotoxic T cells. Cytotoxic T cells cause damage and inflammation. IFN-α promotes a Th1 immune response pattern that increases IFN-γ and interleukin 2. This is pro-inflammatory and induces HT. A Th1 to Th2 mediated immune process transition promotes Graves’ hyperthyroidism [23].

**Cytotoxic T-lymphocyte antigen 4 and programmed cell death protein 1 inhibition-induced thyroid dysfunction**

CTLA4 is cytotoxic T-lymphocyte antigen 4 and PD-1 is programmed cell death protein 1. Both are cell surface receptor on T cells which down-regulate immune response (immune checkpoints). Immunomodulatory agents used to treat melanoma inhibit these pathways and activate immune response are ipilimumab (via CTLA4 inhibition), pembrolizumab (via PD-1 inhibition), and nivolumab (via PD-1 inhibition) [24].

Ipilimumab is a targeted human immunostimulatory antibody directed against CLT4 which is a major advance in the treatment of advanced melanoma but has side-effects which include rash, colitis, hypophysitis, and thyroiditis. Ipilimumab causes hypophysitis in 8%, and thyroiditis/hypothyroidism in 6% occurring after one to three cycles or longer so it can manifest after 2 weeks up to 3 years of therapy as fatigue and painless thyroiditis. The combination of ipilimumab and nivolumab with inhibition of both CLT4 and PD-1 is more potent with thyroiditis in 22% which can be associated with a hyperthyroidism to hypothyroidism transition. The glucocorticoid responsiveness of this thyroid disease is unclear [25].

**Alemtuzumab-induced thyroid disease**

Alemtuzumab is indicated for the treatment of relapsing-remitting forms of multiple sclerosis for patients with active disease defined by clinical or imaging features to slow the accumulation of physical disability and reduce the frequency of clinical relapses. It is a humanised monoclonal antibody to CD52 a protein expressed at high levels on the surface of B and T lymphocytes. It is administered as a series of intravenous doses (12 mg daily for 5 consecutive days) that can be repeated after 12 months. The mechanism of action is proposed to be immune depletion via antibody-mediated cell cytolyis and complement-mediated lysis then immune reconstitution with permanently altered immune function [26]. Alemtuzumab treatment increases the risk of autoimmune diseases.AITD occurs in up to 36% of patients over 48 months from first exposure with serious events in up to 1% [27]. Other autoimmune diseases that are increased are immune thrombocytopenic purpura in 1% and nephropathy mainly anti-glomerular basement membrane glomerulonephritis in 0.3% [28].

Annual incidence of the first episode of thyroid dysfunction following alemtuzumab treatment peaks in the third year after first administration at 16.1% [27]. Hyperthyroid Graves’ disease is the most common manifestation of AITD. Overt Graves’ hyperthyroidism can spontaneously resolve. A low incidence of ophthalmological adverse events has been observed. It is recommended that 3 monthly monitoring of thyroid function should continue for 4 years from the last dose of alemtuzumab. Patients with positive baseline anti-TPO antibodies had an increased risk of developing thyroid disorders; however, the majority of patients who developed a thyroid disorder were anti-TPO antibody negative at baseline. Therefore, regardless of pretreatment anti-TPO antibody status patients may develop a thyroid adverse reaction and should have all required tests performed periodically.

Thyroid carcinoma has been identified in the trials of alemtuzumab in multiple sclerosis. However this may well be due to ascertainment bias as the small number found have all been less than 20 mm diameter and most have been papillary microcarcinomas incidentally discovered at routine ultrasonography or at thyroidectomy for Graves’ disease.

**PAPILLARY THYROID CARCINOMA AND HASHIMOTO’S THYROIDITIS**

The relationship between PTC and HT is still unclear. A meta-
analysis of 38 eligible studies (10,648 PTC cases) found histologically proven HT in 2,471 PTCs (23.2%) [29].

HT was more frequently observed in PTC than in benign thyroid diseases and other carcinomas (odds ratio [OR], 2.8 and 2.4; \( P < 0.001 \)). The authors concluded that PTC is significantly associated with pathologically confirmed HT and that patients with HT need to be carefully monitored for the development of PTC.

However Jankovic et al. [30] reported there is no clear evidence to support the correlation between HT and PTC. They noted that many studies of thyroidectomy specimens report a positive relationship and there are many studies in the literature that propose a genetic link between HT and PTC involving the phosphoinositide 3-kinase/Akt pathway and receptor tyrosine kinase RET/PTC gene rearrangements, but population-based cytological studies did not find a statistically significant correlation between HT and PTC, although these studies were limited by the lack of definitive pathology. Conversely thyroidectomy studies, which reported a statistically significant positive correlation, are subject to selection bias. Thus more prospective studies with longer follow-up are needed to further elucidate this relationship.

Caturegli et al. [31] in a study using the surgical pathology records of Johns Hopkins Hospital found that the increased incidence of papillary thyroid cancer observed in recent years was paralleled by increases in the form of papillary thyroid cancer associated with HT and suggested that these findings indicate that papillary thyroid cancer is the initial lesion, which then induces a lymphocytic infiltration that in some patients progresses to established HT.

Fiore et al. [32] suggest that the different epitope patterns of Tg Ab inAITD and non-AITD patients supports the hypothesis that two different autoimmune mechanisms may be involved, one typical of AITD and the other of an immune reaction to PTC, and that thyroid function may also affect the frequency of PTC with the risk of cancer increasing with serum TSH levels. They found raised TSH was a stronger independent predictor of malignancy in HT (OR, 66.5) than the presence of Tg Ab (OR, 2.0).

SELENIUM FOR THYROID DISEASE

Most speculation on a therapeutic role of selenium relates to HT rather than Graves’ disease, but so far the only definite efficacy for selenium in autoimmune is in mild/moderate Graves’ ophthalmopathy [33].

Selenium is yet be tested in Graves’ hyperthyroidism but a trial has been established in Europe to do this, the selenium supplementation for patients with Graves’ hyperthyroidism (GRASS) trial: 200 \( \mu \)g daily for 24 to 30 months with a primary endpoint of proportion with ATD failure [34]. Similarly selenium is to be tested in chronic autoimmune thyroiditis in the Chronic Autoimmune Thyroiditis Quality of Life Selenium Trial (CATALYST) trial of 200 \( \mu \)g daily for 12 months with the primary endpoint of quality of life [35].

SMALL MOLECULE LIGAND THYROID-STIMULATING HORMONE RECEPTOR AGONIST AND ANTAGONISTS

SML agonists which activate receptors, SML neutral antagonists, which inhibit receptor activation by agonists, and SML inverse agonists which inhibit receptor activation by agonists and inhibit basal or constitutive, agonist independent signaling have been identified [36]. TSH-receptor stimulatory antibodies (TSAbs) bind to the extracellular domain of the TSH-receptor but SML antagonists bind to the transmembrane domain; thus, it is likely that signal transduction initiated by the majority of TSAbs can be blocked by SML. SML antagonism of TSAb could treat Graves’ hyperthyroidism and Graves’ ophthalmopathy.

Turcu et al. [37] have reported the \textit{in vitro} effect of an SML antagonist (NCGC 00242595, a neutral antagonist) to inhibit TSH receptor antibody-induced orbital fibroblast functions in involved in the pathogenesis of Graves’ ophthalmopathy, with reduction of antibody-induced cyclic AMP, phospho-Akt protein (pAkt), and hyaluronan production.

ASPECTS OF THE MANAGEMENT OF HASHIMOTO’S THYROIDITIS AND HYPOTHYROIDISM

The management of HT depends on the clinical picture. In general the choice is between observation and thyroxine replacement therapy. Although glucocorticoid therapy can modulate the thyroiditis and acutely improve thyroid function the risk associated with the dose and duration of such therapy is considered to outweigh the benefit. Short-term use of prednisolone has been reported to have longer term benefit in IgG4-disease associated HT [38].

The presence of thyroid antibodies in the absence of either subclinical or overt hypothyroidism should prompt infrequent surveillance, less than yearly. If asymptomatic TSH elevation is present then yearly surveillance is appropriate.
When TSH is >10 mU/L then treatment should be considered, especially as the height of TSH in SCH predicts the speed of evolution to overt hypothyroidism. Relevant symptoms in a patient with a TSH between 5 to 10 mU/L may prompt consideration of thyroxine treatment but not all SCH patients warrant treatment. The elderly above 85 years old with SCH may have a reduced mortality rate and do not experience symptoms such as depression or impaired cognitive function from modestly high TSH [39].

A study in Scotland of general practitioner prescribing of thyroxine in SCH identified an increasing rate of thyroxine prescriptions and a falling TSH threshold for initiation of treatment. At 5 years this produced 10.2% of patients with a low TSH level and 5.8% with a suppressed TSH level. Thus thyroxine treatment of SCH can easily produce iatrogenic subclinical hyperthyroidism with the risk of atrial fibrillation and osteoporosis [40]. The authors argue that data for the increased risk of harm from subclinical hyperthyroidism are stronger than the data for potential benefit from treatment of SCH so that observing the elderly with SCH may be more prudent than treating them.

The recent European Thyroid Association management guidelines for SCH [41] provide useful suggestions for initiation of thyroxine therapy. These guidelines recommend that patients over 70 years of age with a raised TSH less than 10 mU/L should continue to be observed without thyroxine therapy with monitoring every 6 months. Thyroxine therapy should be considered in these patients if clear signs of hypothyroidism emerge or if a high vascular risk exists. In those under 70 years of age with a TSH >10 mU/L then thyroxine therapy is recommended, and if TSH is <10 mU/L with hypothyroid symptoms then a 3-month trial of thyroxine therapy should be instituted and continued if the clinical response is positive.

CONCLUSIONS

The management of autoimmune thyroid disease continues to be revised by new research which includes the identification of new entities, such as IgG4-related thyroid disease and new drug-induced forms of thyroid disease; the development of novel small molecules capable of influencing mechanisms of autoimmunity; and more detailed knowledge of the risks versus benefits of thyroxine therapy in subclinical hypothyroidism.

CONFLICTS OF INTEREST

The author has been a presenter at a Sanofi-Aventis (Genzyme) seminar to neurologists on alemtuzumab (Lemtrada) and received an honorarium for this.

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