to the hypothyroid phase of illness. 5 patients (3 trans masculine and 2 trans feminine) demonstrated hyperthyroidism, 4 of whom had Graves' Disease. 2 patients had multinodular goiter, both trans masculine. 2 patients had thyroid malignancies, both trans feminine, of whom one had proven follicular thyroid carcinoma and the other had unspecified thyroid malignancy. Among hypothyroid patients, there was a slight non-significant trend toward increased thyroid hormone requirements while receiving treatment with estradiol or testosterone. **Conclusion:** To our knowledge, this represents the first attempt to characterize the prevalence of various thyroid disease states in the gender diverse population. Our data corresponded to a prevalence of hypothyroidism of approximately 8.7%, which is higher than previously published estimates of 3-5% in the general population. Whether this represents actual increased prevalence or assessment bias is uncertain. It is important for all health professionals who care for gender diverse people to identify and appropriately treat thyroid disease, and to monitor thyroid function closely if gender-affirming hormone therapy is initiated.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Comparison of Block and Replace Regime and Titration Regime in Graves' Disease

Cho Mar, C.Mar, M.Med Sc(Int. Med), FRCPE, Dr.Med.Sc(Endocrinology).
University of Medicine 1, Yangon, Myanmar.

In Graves' disease (GD), medical treatment is still the cornerstone in its management and there were some studies done on comparison of the block and replace regime and titration regime of the antithyroid drugs (ATDs). In Myanmar, titration regime is mostly practiced for management of GD. In daily clinical practice, frequent hospital visits are needed in titration regime and loss of follow-up is an obstacle in patients treated with titration regime. A hospital based randomized clinical trial was conducted and aimed to compare the proportion of attainment of euthyroid status between block and replace regime and titration regime in patients with recently diagnosed GD. A total of 117 patients; 58 patients in block and replace regime and 59 patients in titration regime, who met the inclusion criteria were included. The results showed that euthyroid status was observed in increasing trend during the study period for both regimes but there was no significant difference of achieving euthyroid status between the regimes at the end of 12 months. Regarding side effects of ATDs, skin rash and pruritus were more frequently occurred during the first 3 months of ATDs but no significant difference was noted between the regimes at the end of study. There was also no case of serious side effects such as agranulocytosis and hepatotoxicity up to the end of 12 months. The results of the study pointed out that block and replace regime was comparable to dose titration regime in attaining euthyroid status. As a conclusion, block and replace regime can be applied as an alternative option where titration regime is not feasible. **Reference:** (1) Abraham *et al*., 2005; A systematic review of drug therapy for Graves' hyperthyroidism. *Eur J Endocrinol*. 153: 489-98. (2) Vaidya *et al*., 2014; Block & replace regime versus titration regime of antithyroid drugs for the treatment of Graves' disease: a retrospective observational study. *Clinical Endocrinology*. 81: 610–613.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Does Primary BCG Vaccination Prevent Autoimmune Hypothyroid Disease?

Kanhaiya Agrawal, MD, Preetam Basak, MSc, Pinaki Dutta, D.M., Rama Walia, DM, Anil Bhansali, DM, Naresh Sachdeva, PhD.
Department of Endocrinology, Post graduate institute of medical science, Chandigarh, India.

Autoimmune thyroid disease (AITD) involves autoimmune destruction of thyrocytes marked by the presence of anti-TPO and/or anti-TG antibodies. In autoimmune diseases, an immunomodulatory role of BCG vaccination has been reported with decreased autoantibody production and induction of regulatory T cells (Tregs). We hypothesize that the loss of efficacy of BCG vaccine in adulthood might be associated with the appearance of AITD. To evaluate the protective efficacy of primary BCG vaccination, we assessed the anti-mycobacterial responses, thyroid function, and antithyroid autoimmune responses in autoimmune subclinical hypothyroid (SCH) (n=39) and non-autoimmune SCH (n=25) subjects. The anti-mycobacterial responses were determined by the Mantoux test and by BCG induced *in-vitro* proliferation of peripheral blood mononuclear cells in terms of proliferation index (PI). The immunophenotyping of autoreactive CD8+ T cells recognizing TPO derived epitopes was performed by flow cytometry using APC labelled dextramers by flow cytometry in patients with HLA-A*02 and HLA-A*24 alleles. We observed that the autoimmune SCH group had more subjects with a negative Mantoux reaction (less than 5mm) (61.5% vs 33.3%, p= 0.01). The PI with BCG stimulation was similar in both groups (2.55±0.31 vs 2.51±0.41, p = 0.667). The correlations (r) between Mantoux test and PI in autoimmune SCH and non-autoimmune SCH were, insignificant. The autoimmune SCH group had more subjects with diffused thyroiditis (43% vs 13%, p= 0.02). The SCH subjects with the presence of a BCG scar (n=11) had lower TSH (μIU/ml) (7.94±1.67 vs 6.75±1.56, p= 0.026) levels and lower frequencies of TPO-reactive CD8+ T cells (3.35±0.72% vs 1.77±0.98%, p= 0.061), as compared to subjects with the absence of a BCG scar (n = 53). The SCH subjects with positive Mantoux test (more than 10mm) demonstrated similar titres of anti-TG antibody (IU/ml) [(230 (56.71-508.90) vs 85.5 (15-345.9), p= 0.055] and anti-TPO antibody (IU/ml) [29.9 (5-135) vs 12 (5-83), p= 0.665)] as compared to those with a negative Mantoux test. The TPO-reactive CD8+ T cells and anti-TG antibody titres had a negative correlation in autoimmune SCH (r= -0.695, p=0.038) and non-autoimmune SCH (r= -0.642, p=0.024) subjects. Next, we observed a similar frequency of TPO-reactive CD8+ T cells in non-autoimmune and autoimmune SCH subjects (8.40±3.74% vs 9.02±4.17% p= 0.937). The absence of anti-TPO or anti-TG antibody did not rule out the presence of any underlying autoimmunity. The persistence of the protective effects of either BCG

vaccination or exposure to *Mycobacterium species* might be involved in modulating autoimmune responses towards the thyroid gland. Our study warrants further research on the immunomodulatory role of BCG in adult subjects with a family history of autoimmune diseases including AITD.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Evaluation of TRAb and TSI Leves and Thyroid Function in Pregnant Women With Graves' Disease and Newborn: Preliminary Data

Maurício Massucati Negri, MD[1], Paula Bruna Mattos Coelho Araujo, MSc[2], Dalva Margareth Valente Gomes, MSc[2], Maria Fernanda Miguens Castelar Pinheiro, PhD[2], Yolanda Schrank, MSc[2], Andrea Faria Dutra Fragoso Perozo, MD[2], Suemi Marui, PhD[3], Rosita Fontes, PhD[2].
[1]IEDE, Rio de Janeiro, Brazil, [2]DASA, Rio de Janeiro, Brazil, [3]DASA, USP, São Paulo, Brazil.

Introduction: GD, mediated by TSH receptor-stimulating immunoglobulins (Igs) (rTSH), can lead to fetal thyroid dysfunction through the passage of Igs through the placenta during pregnancy. TRAb levels, used for prognostic evaluation, measure rTSH-stimulating and blocking Igs while TSI evaluates only as stimulating Igs. Objective: To prospectively evaluate pregnant women with DG and newborns (NB) by measuring TRAb and TSI and their correlation with thyroid function and postpartum complications. **Methods:** The patients were evaluated during pregnancy and the puerperium and the respective newborns. TSH, thyroid hormones and TRAb were evaluated by electrochemiluminescent method (Roche) and TSI by chemiluminescent assay (Siemens). TRAb<1.75IU/L and TSI<0.55IU/L were considered negative. **Results:** Nine patients were evaluated, with a mean age of 27.4±5.7 years: 6 had TRAb and TSI positive in the 1st trimester (1st-tri), when they maintained or started DAT; one with both negative (without DAT) and one with weakly positive TSI, when DAT was suspended. These last two remained euthyroid during pregnancy and puerperium. Of the first 6, 4 were evaluated in the 3rd-tri: three negative for TRAb and maintained positive TSI, 2 in low leves and one for high titles, when DAT was suspended or reduced; one kept both at very high levels. A patient with post-DT hypothyroidism, performed 3 years ago, using levothyroxine, evaluated in the 3rd-tri, had a negative TRAb and a highly positive TSI and remained so after pregnancy. The two patients who presented weakly positive TSI in the 3rd-tri evolved with their negative results and without DAT in the puerperium. The patient with TSI in high titers evolved with elevated levels as well as positive TRAb titers and postpartum decompensation. The patient with positive antibodies remained compensated for stable doses of DAT. Four NB were evaluated: all healthy, with normal thyroid function and negative TRAb. TSI was positive in 2 in the postpartum period; TSI was negative afterwards, while in the other 2 both antibodies were negative. **Conclusions:** TSI was not associated with thyroid dysfunction in NB, although it was associated with worsening hyperthyroidism in pregnant women, when at high titers. Positive TSI at low levels were not associated with worsening of the condition, which requires further studies to determine the cutoff point for assessing treatment suspension.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Hearing Loss and Teprotumumab

Andrea Kossler, MD, FACS[1], Connie Martin Sears, M.D.[2], Chrysoula Dosiou, MD, MS[3].
[1]Stanford University, Menlo Park, CA, USA, [2]Stanford University, Palo Alto, CA, USA, [3]Stanford University School of Medicine, Atherton, CA, USA.

Thyroid eye disease (TED) is an unpredictable autoimmune inflammatory disease which can be sight-threatening, debilitating, and disfiguring. Teprotumumab (IV infusion every 3 weeks x 8 doses) was recently approved as the first and only FDA-approved drug for TED in 2020. Phase 2 and 3 studies showed significant improvement in proptosis, double vision, soft tissue inflammation and quality of life for patients with active moderate to severe TED. Side effects were experienced by 85% of patients on teprotumumab. Hearing loss symptoms were reported in 10% of patients and were reported to be reversible upon stopping the drug. Objective: To explore the incidence of hearing loss symptoms and sensorineural hearing loss in patients treated with teprotumumab. **Methods:** All patients, followed at one institution, treated with at least 4 infusions of teprotumumab were evaluated. Charts were evaluated for baseline hearing symptoms and hearing symptoms during or after therapy with teprotumumab. Those patients with hearing symptoms were referred for audiogram testing and patulous eustachian tube (PET) testing. **Results:** Twenty-eight patients were included in this analysis. Thirteen patients (46%) complained of hearing symptoms. The most common symptoms were autophony or an ear plugging sensation and hearing loss or muffled hearing. Hearing symptoms developed after a mean of 3.6 infusions. Of the patients with hearing symptoms, three patients (23%) had sensorineural hearing loss documented on audiogram (n=2) or patulous eustachian tube (n=1) documented on PET testing. To date, the patient with PET has experienced some improvement, but not resolution, of her symptoms. The two patients with documented sensorineural hearing loss have not experienced a significant improvement in hearing, on audiogram, on average 3 months after stopping teprotumumab. **Conclusion:** Teprotumumab is a promising new therapy for active moderate to severe thyroid eye disease. Providers should consider performing a baseline audiogram with PET testing and performing audiograms with PET testing for patients that develop hearing symptoms during or after therapy. Hearing loss is a concerning adverse event and its mechanism and reversibility should be further studied.

Thyroid

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