optic neuropathy or exposure keratopathy and (5) chronic TED greater than 9 months. In our series, we found that teprotumumab was as effective in a wider population of chronic TED patients than included in the clinical trials.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

The Immune Microenvironment of Hashimoto's Thyroiditis Regulates the Glycosylation Modification of IgG

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Objectives: Elevation of anti-thyroglobulin antibodies that are primarily IgG isotype is a hallmark of Hashimoto's thyroiditis (HT). As for IgG,it bears two conserved repertoire of N-linked glycans attached to its crystallizable fragment (Fc) at the 297 asparagine residue (Asn297). In our previous study, we found that serum TgAb IgG from HT patients exhibits higher glycosylation levels than those observed from healthy controls. Previous studies confirmed that imbalance of Th1/Th2 and Th17/Treg leading to altered immune microenvironment with elevation of certain cytokines was found in the thyroid tissue of HT, including IFN-γ, TNF-α, IL-21, IL-17A, IL-6, BAFF, APRIL. Thus, the aim of our study was to investigate the influence of the elevated cytokines on the differentiation process of B cells and the glycosylation levels of IgG. **Methods:** We formed a two-phase culture system in vitro to promote B cells to differentiate to antibody-secreting cells (ASCs). In the process of cell culture, B cells were co-cultured with cytokines as followed: IFN-γ, TNF-α, IL-21, IL-17A, IL-6, BAFF and APRIL. Flow cytometry was performed to identify the percentage of plasmablasts ($CD38^{+}CD27^{high}$) and plasma cells ($CD20^{-}CD138^{+}$). ELISA was used to measure the yield of IgG in culture supernatants. The glycosylation levels of secreted IgG under different stimulation conditions were detected by lectin microarray. **Results:** We found that IL-21, TNF-α and BAFF can significantly promote the differentiation of B cells into ASCs in vitro culture system, and augment the production of IgG to over 4-fold. In addition, cytokines affected the glycosylation modification profile of IgG diversely: 1) IL-21, IL-17A, TNF-α, BAFF significantly increased the glycosylation level of sialic acid of total IgG; 2) IFN-γ significantly increased the level of galactose; 3) IL-21, IL-17A, IFN-γ, BAFF, and APRIL significantly increased the level of mannose; 4) IL-6 significantly decreased the level of sialic acid, galactose and mannose; 5) IL-17A, IFN-γ, TNF-α, BAFF significantly increased the level of GalNAc that was a component of O-Glycan,which only exists in the hinge region of IgG3 subclass. **Conclusions:** The abnormally elevated cytokines in microenvironment participated in the regulation of B cell terminal differentiation process and glycosylation level of IgG, thereby involving in the pathogenesis of AITD.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

The Potential Impact of the COVID-19 Pandemic on Clinical Management of Thyroid Disorders in Japan.

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Background: The indirect influence of the coronavirus disease 2019 (COVID-19) pandemic on clinical practice has received great attention. However, the evidence about how the pandemic has affected clinical management of hypothyroidism and hyperthyroidism, two common diseases worldwide, is lacking. We therefore aimed to examine the trends in the number of outpatients with thyroid disorders and their thyrotropin (TSH) levels before and during the pandemic in Japan. **Methods:** This cohort study included all patients aged ≥20 years who visited Ito Hospital, one of the largest hospitals that specialize in thyroid disorders in Japan, during 2019/1-2020/6. Our outcomes of interest were 1) trends in the aggregated number of visits at the clinic and 2) trends in average TSH levels from January 2019 to June 2020. The trends in TSH according to the clinic visit in early 2020 were assessed utilizing difference-in-difference models controlling for age, sex, and city of residence, stratified by each medication use (i.e., levothyroxine [LT4], antithyroid drug [ATD], potassium iodine [KI], or no medication). **Results:** During 2019/1-2020/6, we observed 517,412 visits at Ito Hospital for thyroid disorders, and the average number of visits per month was significantly decreased for both the first visits (1,995 in 2019 vs. 1,268 in 2020; reduction rate, 36%; $p<0.001$) and the follow-up visits (29,509 in 2019 vs. 21,959 in 2020; reduction rate, 26%; $p<0.001$). Among 15,455 patients who had been followed in 2019, we found a higher TSH at the follow-up visits during 2020/4-2020/6 among patients with LT4 who did not visit the clinic during 2020/1-2020/3 than those who did (difference-in-difference [95%CI]=+1.77 [1.25-2.29], $p<0.001$). We also found decreased trends in TSH among patients with ATD or KI who visited the clinic during 2020/1-2020/3 ($p<0.001$ for both categories), but not among patients with no medications ($p=0.29$). **Conclusions:** In this large cohort in Japan, we found the decreased number of outpatients with thyroid disorders since 2020/1 with a nadir in 2020/4. Using individual-level data, we also found the association between visiting the clinic in early 2020 and TSH control at the following visit among patients with medications. These findings highlight the importance of careful monitoring of patients with medications for thyroid disorders during the COVID-19 pandemic.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

The Synergistic Effect of Corticosteroids and Mycophenolic Acid on Chemokines in Orbital Cells From Patients With Graves' Ophthalmopathy

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In recent studies, an improvement of the response rate to therapy has been reported with corticosteroids and mycophenolic acid in patients with Graves' ophthalmopathy (GO). In GO, retro-orbital cells (fibroblasts, preadipocytes, and extraocular muscle cells) secrete Th1 and Th2 chemokines stimulated by cytokines. Until now, no studies are present in literature regarding the effect of corticosteroids and mycophenolic acid on the secretion of chemokines in GO orbital cells. For this reason, the effect of increasing concentrations of mycophenolic acid or corticosteroids on the secretion of either the Th1 (CXCL10) and Th2 (CCL2) chemokines was tested in primary cultures of myoblasts, preadipocytes and fibroblasts obtained from GO patients. CXCL10 was undetectable in the supernatants of the retro-orbital cells in primary cultures; its release was induced dose-dependently by IFNγ, while TNFα alone had no effect. On the contrary CCL2 release (that was produced in low amounts basally) was dose-dependently induced by TNFα, while IFNγ alone had no effect. In both cases the combination of TNFα and IFNγ had a significant synergistic effect on CXCL10 and CCL2 secretion. The release of these chemokines was dose-dependently inhibited by increasing concentrations of mycophenolic acid, or corticosteroids (in a pharmacological range), in presence of IFNγ and TNFα stimulation. Moreover, the association of corticosteroids and mycophenolic acid (in presence of IFNγ and TNFα) had a stronger inhibitory effect on the chemokines release. In conclusion, in GO orbital cells, mycophenolic acid and/or corticosteroids (in a pharmacological range) have an inhibitory role on the secretion of both Th1 (CXCL10) and Th2 (CCL2) chemokines. This suggests a possible therapeutic role of these drugs.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Thyroid Autoimmunity Following Alemtuzumab Treatment in Multiple Sclerosis Patients

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Alemtuzumab, a humanized anti-CD52 monoclonal antibody, is approved for the treatment of highly active relapsing-remitting multiple sclerosis (MS). The principal adverse effect is the development of secondary autoimmune disorders during the immune reconstitution period after alemtuzumab, with autoimmune thyroid disease (AITD) being the most common. To define the type, timing and course of AITD after alemtuzumab treatment for MS we analyzed clinical and serologic data from 31 patients (follow-up range 8 to 58 months). Hashimoto thyroiditis (HT) with positive anti-TPO and/or anti-Tg antibodies was present at baseline in four patients. Of note, one of them 13 months after the first dose developed mild hyperthyroidism [stimulating TRAbs: 1,8U/L, normal range:<0,1] with subsequent spontaneous shift to hypothyroidism within two months. Of 26 patients without previous history of thyroid dysfunction, 17 (65,3%) developed adverse thyroid events, principally Graves' disease (GD) with positive stimulating TRAbs (n=10, 58,8%) after a mean of 22,4 months following the first alemtuzumab course. Half of the GD cases exhibited fluctuating thyroid status, transitioning from hyperthyroidism to hypothyroidism and vice versa. Most of them were started on block and replace antithyroid drug (ATD) treatment. Three GD patients are currently under treatment with ATD in a dose-reducing regimen. Two patients developed Graves' ophthalmopathy. One of them underwent total thyroidectomy and 27 months post-surgery TRAbs are still positive. One patient developed hypothyroidism associated with surprisingly high stimulating TRAbs (>40 U/L) as well as anti-Tg antibodies. Seven cases of HT with positive anti-TPO/anti-Tg antibodies were documented, of which one developed hypothyroidism. During follow-up, two successful pregnancies were recorded. The first, a 32-year-old woman, developed HT with hypothyroidism 12 months after the first cycle of alemtuzumab and gave birth to a healthy boy 22 months following last dose. The second, a 31-year-old woman, developed GD hyperthyroidism during the first trimester of pregnancy and was started on PTU that was stopped in the beginning of the second trimester. TRAbs titer declined and a healthy girl was delivered. Contrary to published literature, we recorded frequent occurrence of GD with fluctuating and unpredictable course requiring block and replace ATD regimen. This is suggestive of alternating stimulating and inhibitory TRAbs, while further studies are needed to understand the underlying mechanisms responsible for Th1-Th2 balance and cytokine pathways towards AITD. Pretreatment screening and careful follow-up allow for early diagnosis and treatment. Finally, concerning future pregnancies post-alemtuzumab it is important to address the risk for secondary AITD in women of childbearing age in conjunction with their treating obstetrician.

Thyroid

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