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.

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Thyroid Function Before, During and After COVID-19

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Context: The effects of COVID-19 on the thyroid axis remain uncertain. Recent evidence has been conflicting, with both thyrotoxicosis and suppression of thyroid function reported. **Objective:** We aimed to detail the acute effects of COVID-19 on thyroid function and determine if these effects persisted upon recovery from COVID-19. **Design:** Cohort observational study. **Participants and Setting:** Adult patients admitted to Imperial College Healthcare National Health Service Trust, London, UK with suspected COVID-19 between March 9 to April 22, 2020 were included, excluding those with pre-existing thyroid disease and those missing either free thyroxine (FT4) or TSH measurements. Of 456 patients, 334 had COVID-19 and 122 did not. **Main Outcome Measures:** TSH and FT4 measurements at admission, and where available, those taken in 2019 and at COVID-19 follow-up. **Results:** Most patients (86·6%) presenting with COVID-19 were euthyroid, with none presenting with overt thyrotoxicosis. Patients with COVID-19 had a lower admission TSH and FT4 compared to those without COVID-19. In the COVID-19 patients with matching baseline thyroid function tests from 2019 (n=185 for TSH and 104 for FT4), both TSH and FT4 were reduced at admission compared to baseline. In a complete cases analysis of COVID-19 patients with TSH measurements at follow-up, admission and baseline (n=55), TSH was seen to recover to baseline at follow-up. **Conclusions:** Most patients with COVID-19 present with euthyroidism. We observed mild reductions in TSH and FT4 in keeping with a non-thyroidal illness syndrome. Furthermore, in survivors of COVID-19, thyroid function tests at follow-up returned to baseline.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Thyroid Immune-Related Adverse Events Among Cancer Patients Treated With Combination of Anti-PD1 and Anti-CTLA4 Immune-Checkpoint Inhibitors: Clinical Course and Outcomes

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Introduction: Thyroid immune-related adverse events (irAEs) have been reported to have prognostic significance among cancer patients treated with anti-PD1 and anti-PDL1 monotherapies. There are scanty data in the literature thus far about the clinical course and prognostic significance of thyroid irAEs in the routine clinical use of combination anti-PD1/anti-CTLA4 treatment in advanced cancer patients. We evaluated the clinical course and predictors of thyroid irAEs, in relation to outcomes of advanced cancer patients treated with combination anti-PD1/anti-CTLA4. **Method:** We conducted a territory-wide study and identified advanced cancer patients who received ≥1 cycle of combination anti-PD1/anti-CTLA4 between 2015 and 2019 in Hong Kong. Patients were excluded if (i) they had a history of thyroid disorder or thyroid cancer, (ii) immune checkpoint inhibitor-related endocrinopathies occurred before the commencement of combination anti-PD1/anti-CTLA4, (iii) they were on concurrent tyrosine kinase inhibitor (TKI), (iv) baseline thyroid function tests (TFTs) were absent or abnormal, and (v) the duration of follow-up was <30 days. TFTs were monitored every three weeks. Thyroid irAE was defined by ≥2 abnormal TFTs after initiation of combination anti-PD1/anti-CTLA4 in the absence of other causes. The initial presentation was classified into hypothyroidism (overt if TSH >4.8 mIU/L and fT4 <12 pmol/L; subclinical if TSH >4.8 mIU/L and fT4 12-23 pmol/L) and thyrotoxicosis (overt if TSH <0.35 mIU/L and fT4 >23 pmol/L; subclinical if TSH <0.35 mIU/L and fT4 12-23 pmol/L). **Results:** One hundred and three patients were included (median age: 59 years; 71.8% men). Around half of patients had hepatocellular carcinoma. About 45% had prior anti-PD1 exposure. Upon median follow-up of 6.8 months, 17 patients (16.5%) developed thyroid irAEs, where 6 initially presented with thyrotoxicosis (overt, n=4; subclinical, n=2), and 11 with hypothyroidism (overt, n=2; subclinical, n=9). Eventually, 10 patients (58.8%) required continuous thyroxine replacement. Systemic steroid was not required in all cases. Prior anti-PD1 exposure (OR 3.67, 95% CI 1.19-11.4, p=0.024) independently predicted thyroid irAEs. Multivariable Cox regression analysis revealed that occurrence of thyroid irAEs was associated with better overall survival (adjusted hazard ratio 0.39, 95% CI 0.19-0.79, p=0.009), independent of prior exposure to anti-PD1 (p=0.386) and prior TKI exposure (p=0.155). **Conclusion:** Thyroid irAEs are common in routine clinical practice among advanced cancer patients treated with combination anti-PD1/anti-CTLA4, and might have potential prognostic significance. Regular TFT monitoring is advised for timely treatment of thyroid irAEs to prevent potential morbidities.

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Thyroid Immune-Related Adverse Events Are Associated With Improved Survival in Cancer Patients

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