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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