**Thyroid dysfunction after Alemtuzumab treatment**

**for multiple sclerosis: a report of four cases**

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# Introduction

Alemtuzumab (Lemtrada ®) is a humanized monoclonal antibody against CD52, located on the surface of lymphocytes. It is used in the treatment of relapsing-remitting multiple sclerosis (RRMS). The most frequently reported autoimmune disorders observed with alemtuzumab involve the thyroid gland, followed by immune thrombocytopenia and nephropathies. Interestingly, this drug can induce autoimmune thyroid diseases in up to a third of RRMS patients. The physiopathology is incompletely understood but may be related to the pattern of T- and B-cell depletion and repopulation following alemtuzumab treatment. We report our experience in treating these complications in four patients who received Alemtuzumab for RRMS.

# Case report

A 28 years old woman diagnosed with multiple sclerosis (MS), received 5x12mg of Alemtuzumab in 2015 and then three doses in 2016. Hashimoto thyroiditis was diagnosed in August 2017 with hypothyroidism. (TSH 21.01 mU/L, free T4; 4.6 pmol/L, positive Thyroperoxidase-TPO- antibodies)

A second 43 years old woman with goiter and MS, received Alemtuzumab in March 2016 and 2017 (five doses each time). In May 2018, she suffered transient hyperthyroidism associated with an echographic pattern of thyroiditis, followed by hypothyroidism, needing a levothyroxine treatment. The anti-TPO and anti-thyroglobulin antibodies were positive (54.7 U/mL and 162.8 U/mL respectively)

The third patient was a 32 years old woman with MS, that received Alemtuzumab in April 2015 and 2016 (5 and 4 doses). Hypothyroidism was diagnosed in March 2017, and supplementation by Levothyroxine was introduced. Then, in March 2018, transient hyperthyroidism led to discontinuation of thyroid hormone supplementation. Anti-TPO, TSH receptor antibodies and anti-thyroglobulin antibodies were positive. The patient presented later hypothyroidism and was treated with levothyroxine

Our last patient is a 37 years old man diagnosed with RRMS in 2004. In June 2011, he received 5x12mg of Alemtuzumab, then 3x12mg in June 2012. On January 2014, Graves’ disease was diagnosed with hyperthyroidism, and positive anti-TPO and TSH receptor antibodies. He received radioiodine treatment on January 13th, 2014 (15 mCi of iodine 131). In February 2014, hypothyroidism occurred and thyroid hormone supplementation was introduced.

# Discussion

Thyroid related disorders after Alemtuzumab treatment include Graves’s disease, thyroid eye disease, hypothyroidism, and sub-acute thyroiditis. A few cases of thyroid papillary carcinoma were also reported. Individual risk of autoimmunity following alemtuzumab therapy is modified by smoking and family history. As suggested by cases 3 and 4, Alemtuzumab-associated autoimmune thyroiditis is much more likely to be mediated by TSH-receptor-blocking antibodies than in the general population. Interestingly, a conversion from hypo to hyperthyroidism can be observed and should be monitored during follow-up. A literature review suggests that first-line treatment in Graves’ disease after Alentuzumab should consist of antithyroid drugs, although radioiodine as we shown in case 4 ,is also effective.

# Conclusions

Alentuzumab related autoimmune thyroiditis is an interesting model potentially leading to further inside into autoimmune thyroid physiopathology. We report the treatment and a spectrum of autoimmune thyroid side effects following Alemtuzumab treatment, including subacute thyroiditis, Hashimoto thyroiditis and Graves disease without orbital involvement. A thyroid checkup with thyrotropin level measurement is recommended before starting the treatment, then every 3 months up to 48 months after the last dose delivery. We recommend biological monitoring in the long term.