Title: Rapid Remission of Graves' Hyperthyroidism Without Thionamides Under Immunosuppressive Treatment for Concomitant Autoimmune Hepatitis.

Authors: Papadakis GE, Lamine F, Chtioui H, Moschouri E, Christinet MF, Marino L, Favre L, Sciarra A, Sempoux C, Schneider A, Duss FR, Sartori C, Moradpour D, Sykiotis GP

Journal: Thyroid : official journal of the American Thyroid Association

Year: 2018 Feb

Issue: 28

Volume: 2

Pages: 276-278

DOI: 10.1089/thy.2017.0613

Rapid remission of Graves' hyperthyroidism without thionamides under immunosuppressive treatment for concomitant autoimmune hepatitis

Georgios E. Papadakis (1), MD; Faiza Lamine (1), MD; Haithem Chtioui (2), MD; Eleni Moschouri (3), MD; Montserrat Fraga Christinet (3), MD; Laura Marino (1), MD; Lucie Favre (1), MD; Amedeo Sciarra (4), MD; Christine Sempoux (4), MD; Alexandra Schneider (5), MD; Francois-Regis Duss (5), MD; Claudio Sartori (5), MD; Darius Moradpour (3), MD; Gerasimos P. Sykiotis (1), MD PhD

Authors 'affiliations

(1): Service of Endocrinology, Diabetes and Metabolism, Lausanne University Hospital, Lausanne, Switzerland

(2): Division of Clinical Pharmacology, Lausanne University Hospital, Lausanne, Switzerland

(3): Service of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland

(4): University Institute of Pathology, Lausanne University Hospital, Lausanne, Switzerland

(5): Service of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland

Authors' full contact information:

Georgios E. Papadakis: Service of Endocrinology, Diabetes and Metabolism, CHUV, Avenue de la Sallaz 8-10, CH-1011, Lausanne, Switzerland. E-mail: georgios.papadakis@chuv.ch

Faiza Lamine: Service of Endocrinology, Diabetes and Metabolism, CHUV, Avenue de la Sallaz 8-10, CH-1011, Lausanne, Switzerland. E-mail: faiza.lamine@chuv.ch

Haithem Chtioui: Division of Clinical Pharmacology, CHUV, Rue du Bugnon 17, CH-1011 Lausanne, Switzerland. E-mail: haithem.chtioui@chuv.ch

Eleni Moschouri: Service of Gastroenterology and Hepatology, CHUV, Rue du Bugnon 46, CH-1011, Lausanne, Switzerland. E-mail: eleni.moschouri@chuv.ch

Monserrat Fraga Christinet: Service of Gastroenterology and Hepatology, CHUV, Rue du Bugnon 46, CH-1011, Lausanne, Switzerland. E-mail: monserrat.fraga@chuv.ch

Laura Marino: Service of Endocrinology, Diabetes and Metabolism, CHUV, Avenue de la Sallaz 8-10, CH-1011, Lausanne, Switzerland. E-mail: laura.marino@chuv.ch

Lucie Favre: Service of Endocrinology, Diabetes and Metabolism, CHUV, Avenue de la Sallaz 8-10, CH-1011, Lausanne, Switzerland. E-mail: lucie.favre@chuv.ch

Amedeo Sciarra: University Institute of Pathology, Rue du Bugnon 25, CH-1011, Lausanne, Switzerland. E-mail: amedeo.sciarra@chuv.ch

Christine Sempoux: University Institute of Pathology, Rue du Bugnon 25, CH-1011, Lausanne, Switzerland. E-mail: christine.sempoux@chuv.ch

Alexandra Schneider: Service of Internal Medicine, CHUV, Rue du Bugnon 46, CH-1011, Lausanne, Switzerland. E-mail: alexandra.schneider@chuv.ch

Francois-Regis Duss: Service of Internal Medicine, CHUV, Rue du Bugnon 46, CH-1011, Lausanne, Switzerland. E-mail: francois-regis.duss@chuv.ch

Claudio Sartori: Service of Internal Medicine, CHUV, Rue du Bugnon 46, CH-1011, Lausanne, Switzerland. E-mail: claudio.sartori@chuv.ch

Darius Moradpour: Service of Gastroenterology and Hepatology, CHUV, Rue du Bugnon 46, CH-1011, Lausanne, Switzerland. E-mail: darius.moradpour@chuv.ch

Gerasimos P. Sykiotis: Service of Endocrinology, Diabetes and Metabolism, CHUV, Avenue de la Sallaz 8-10, CH-1011, Lausanne, Switzerland. E-mail: gerasimos.sykiotis@chuv.ch

Running title: Glucocorticoids in Graves' disease

Key words: Graves' disease; glucocorticoids; azathioprine; autoimmune hepatitis; TRAb

Dear Editor,

Common management options for Graves' disease (GD) include medical treatment, radioactive iodine (RAI) ablation or surgery. Thionamides (carbimazole, methimazole and propylthiouracil) are the first-line medical treatment of GD. Due to potential hepatotoxicity, their use in the setting of underlying hepatic disease can be challenging. For such cases and if thyroidectomy or RAI cannot be rapidly implemented, alternative medical strategies are not well-established.

We report the case of a 28-year-old Caucasian female diagnosed with type I autoimmune hepatitis (AIH) with severely altered liver function tests (alanine aminotransferase of 1437 U/l, total bilirubin of 286 µmol/l).An undetectable TSH prompted a targeted history that revealed recent restlessness, rapid heartbeat and increased stool frequency. Free thyroxine (fT4) and free triiodothyronine (fT3) were more than 2-fold increased. Ultrasonography showed a normally sized but heterogeneous thyroid with increased vascularity. Autoantibodies against the thyrotropin receptor (TRAb) were strongly positive; a diagnosis of GD was made. Due to the AIH, oral prednisone was started at 50 mg/day, with rapid improvement of hepatic function, allowing for progressive tapering after 2 weeks with concomitant introduction of azathioprine. Given the severe hepatitis, thionamides were withheld in accordance with ATA guidelines recommending caution in case of more than 5-fold transaminase elevation. Propranolol and low dose cholestyramine were prescribed for 3 weeks. A rapid decrease of both fT4 and fT3 was observed as soon as 48 hours after glucocorticoid (GC) initiation. After 1 month of immunosuppressive treatment, liver function tests, fT4 and fT3 were normal. The TRAb titer progressively decreased, becoming negative at 6 months of treatment (**Fig. 1**).

Somewhat paradoxically, GD is one of the few autoimmune diseases for which GCs are not part of the first-line therapeutic choices mainly due to fear of complications from long-term administration. Nevertheless, GCs are routinely used in the management of thyroid storm and have proven effective in combination with carbimazole for resistant thyrotoxicosis.

Improvement of Graves' thyrotoxicosis with GCs was first reported in 1965 by Werner *et al.* who treated 5 GD patients with prednisone 100 mg/day (1). In contrast to our case, some patients in that study had received prior treatment with propylthiouracil. In another study of GD patients (2), the rapid decrease of both T4 and T3 levels by short-term dexamethasone suggested that the GC's benefit is mediated not only by inhibiting the conversion of T4 to T3 in peripheral tissues, but also by reducing thyroid hormone secretion; the present case suggests GC-mediated reduction of TRAb as a potential contributing mechanism. An alteration of the TRAb function and/or type is another possibility, which we were unable to explore because a TRAb bioassay was not performed. Data on the link between GCs and TRAb are scarce. Adding an intrathyroidal dexamethasone injection to methimazole significantly reduced TRAb levels in newly diagnosed GD patients in one study (3). Conversely, Kahaly *et al.* (4) detected a significant decrease of TRAb in patients with Graves' orbitopathy treated by intravenous but not oral GC for 12 weeks. Interestingly, baseline TRAb levels were higher in the latter study, possible suggesting that oral GC might be less effective when the autoimmune load is higher. Other potential explanations for the notable response of TRAb in our case might be the slower tapering, longer treatment and/or the addition of azathioprine.

We chose not to offer immediate definitive treatment to our patient. The risk of immediate total thyroidectomy was estimated too high in a context of acute hepatitis, while RAI

was considered a suboptimal choice given the risk for transient worsening of hyperthyroidism and the possible delayed beneficial effect.

In the absence of an iodine/pertechnetate uptake and scintigraphy, a painless thyroiditis with subsequent normalization of thyroid function cannot be formally excluded. Nevertheless, the ultrasonographic findings and the frankly positive TRAb, measured by a third generation assay render this diagnosis much less likely. Lastly, spontaneous remission may occur, such as in patients with alemtuzumab-induced GD. However, the very rapid pace of improvement of thyroid function as soon as 48 hours after GC initiation argues against spontaneous remission.

In conclusion, this case highlights a potential role for GCs in selected GD patients with contraindications to thionamides who are not eligible for immediate definitive treatment. The onset of GC action in our patient appeared to be rapid, with likely multiple mechanisms, including suppression of T4 conversion to T3 and reduction of TRAb-mediated thyrocyte stimulation. Our observations warrant confirmation in the setting of a clinical trial; treatment with non-GC immunosuppressants could also be explored.

ACKNOWLEDGEMENTS

This work was supported by a Leenaards Foundation Fellowship for Academic Promotion in Clinical Medicine to GPS.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

NAME AND ADRESS OF CORRESPONDING AUTHOR

Corresponding author and person of contact for reprints:

Dr. Gerasimos Sykiotis, Service of Endocrinology, Diabetes and Metabolism

Lausanne University Hospital

Avenue de la Sallaz 8-10, CH-1011, Lausanne, Switzerland

Fax: +41 21 314 94 51. Tel: +41 79 556 14 94. E-mail: gerasimos.sykiotis@chuv.ch

REFERENCES

1. Werner SC, Platman SR 1965 Remission of hyperthyroidism (Graves' disease) and altered pattern of serum-thyroxine binding induced by prednisone. Lancet (London, England) **2**:751–5.

2. Williams DE, Chopra IJ, Orgiazzi J, Solomon DH 1975 Acute effects of corticosteroids on thyroid activity in Graves' disease. J Clin Endocrinol Metab **41**:354–61.

3. Mao X-M, Li H-Q, Li Q, Li D-M, Xie X-J, Yin G-P, Zhang P, Xu X-H, Wu J-D, Chen S-W, Wang S-K 2009 Prevention of relapse of Graves' disease by treatment with an intrathyroid injection of dexamethasone. J Clin Endocrinol Metab **94**:4984–91.

4. Kahaly GJ, Pitz S, Hommel G, Dittmar M 2005 Randomized, Single Blind Trial of Intravenous *versus* Oral Steroid Monotherapy in Graves' Orbitopathy. J Clin Endocrinol Metab **90**:5234–5240.

FIGURE 1

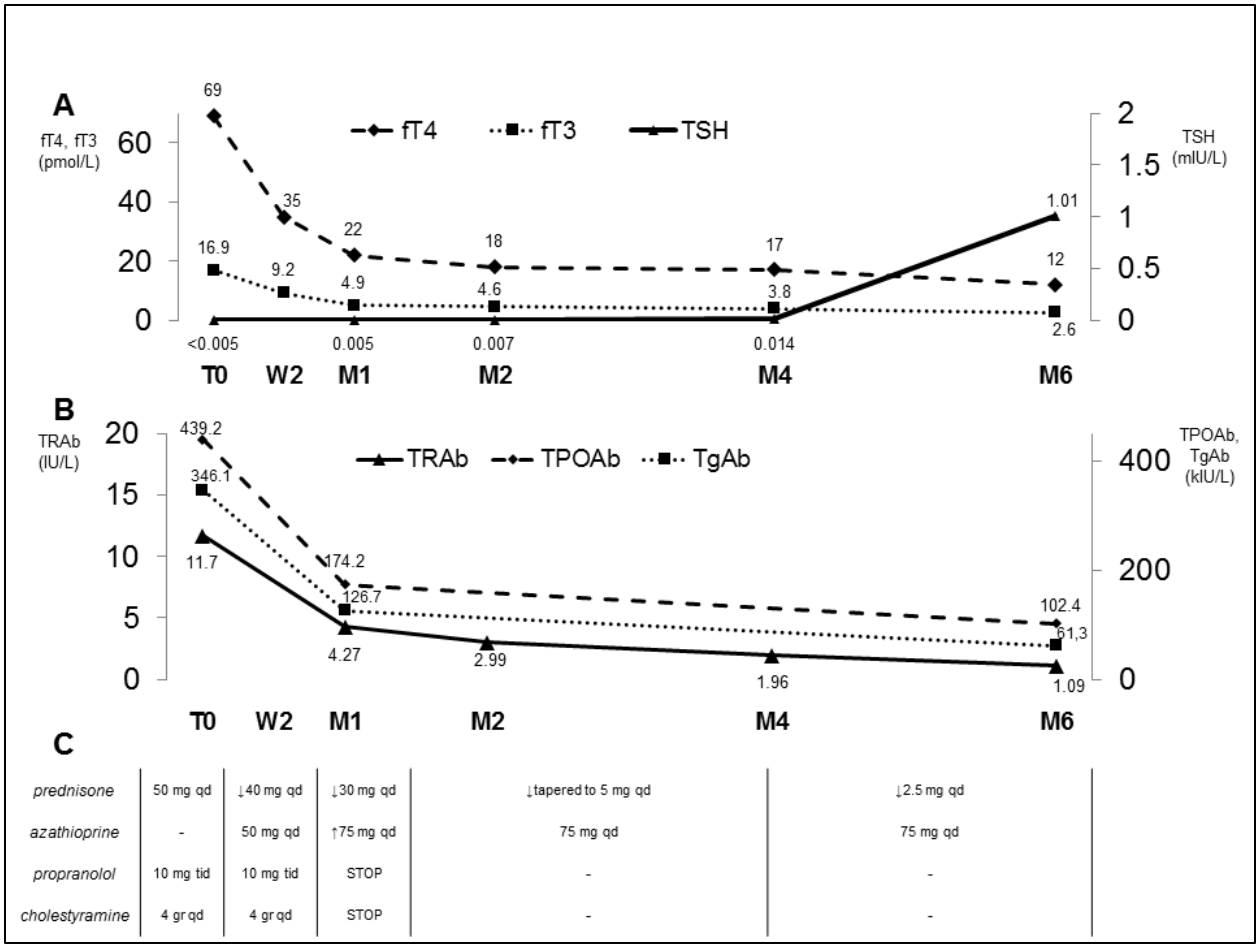

FIGURE 1 LEGEND

Graphical representation of thyroid function tests (A) and thyroid antibodies (B) in different timepoints of the patient's management according to the medications administered (C). Notably, no thionamide treatment was introduced due to concomitant autoimmune hepatitis. A rapid response to prednisone was noted with subsequent normalization of FT4 and FT3 at one month of treatment. Despite tapering of glucocorticoids, the thyroid response was sustained under azathioprine, and TSH and TRAb were normalized at 6 months of treatment. Normal ranges for

the different parameters are the following: TSH, 0.27-4.20 mUI/l; FT4, 12-22 pmol/l; FT3, 3.1-6.8 pmol/l, TRAb, < 1.75 UI/l, TPOAb, < 34 kUI/l; TgAb < 33 kUI/l.

Abbreviations: GC, glucocorticoids; FT4, free thyroxine; FT3, free triiodothyronine; M1, month 1; M2, month 2; M4, month 4; M6, month 6; qd, once daily; T0, right before onset of treatment; tid, three times daily; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; TRAb, thyrotropin receptor antibodies; TSH, thyrotropin; W2, week 2.